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CHRONIC ULCERATIVE COLITIS—AN ALLERGIC DISEASE

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FOR twelve years this writer[13] has gathered evidence that an erythematous, eczematous-like, inflammatory reaction due to food, and less often to pollen and other inhalants and to drug allergy, is the primary cause of chronic ulcerative colitis. Allergy to bacteria and the Sanarelli-Schwartzman reaction also need study, though evidence for this now is lacking.

When allergy is the sole cause, the symptoms and tissue changes gradually reduce or disappear with control of the allergies. When complicating infection, anemia, hypoproteinemia or avitaminosis are present, their treatment along with the control of the allergies is necessary for good results. Severe or fulminating ulcerative colitis can be due to marked food and/or inhalant and possibly drug allergy, with or without the above secondary complications.

Andresen[2] in 1931 first suggested food allergy as the cause of chronic ulcerative colitis. In 1942 he confirmed this opinion in an extended article. Mackey,[9] in 1938, stressed food allergy in the production of this disease, but felt that it was of secondary importance to other major influences. This writer reported allergy especially to foods as the major cause in 1942, and for the first time pollen allergy was found to be responsible for the disease. Other inhalants also were suggested as probable major causes. Since then, confirmation of allergy to foods and less often to pollens was published in 1944,[14] 1947,[17] 1948,[18] and 1949[20] by this writer.

The following favor allergy as a primary cause:

1. Gastrointestinal allergy,[11,13] usually to foods, is very frequent, occurring in any part of the tract from the mouth to the rectum and anus. Local passive transfer in the mucosa of the rectum ileostomies and colostomies have been reported by Gray and Walze[6] and others. Oral and pharyngeal allergy and gastric allergy are common in our experience. Al-

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lergic reactions in various parts of the small and large bowel account for colic, cramping, diarrhea, bleeding, abdominal soreness and pain, fever and other symptoms with varying frequencies. This writer has observed cases of regional enteritis controlled by the elimination of allergenic foods alone. Our experience also indicates that mucous colitis, the irritable bowel, soreness in the colon, constipation and diarrhea, rectal and anal soreness and spasm, a predisposition to hemorrhoids, pruritus ani and a secondary fistulae and abscesses are frequently due to allergy, especially to foods. Psychosomatic causes too frequently are blamed for these symptoms.

2. Allergy best explains the primary lesions of this disease. The erythema, edema and easy bleeding can result from vascular allergy, as they do in atopic eczematous dermatitis. The mucosal granulation similar to that in the skin of atopic eczema is best explained by the multitudinous minute amounts of serum exuding into the mucosa from the allergenically inflamed capillaries. The clinical characteristics, course, and response to proper allergic treatment of cases of atopic dermatitis due to food pollen and other inhalant and drug sensitivities should be observed by all physicians who wish to understand the role of allergy in chronic ulcerative colitis. This continuous serous exudation from the allergically inflamed mucosa and the oozing of blood from the dilated capillaries in the mucosa increase hypoproteinemia.

The herpetic ulcers can arise from minute vascular thromboses, similar to those which cause oral canker sores, which in practically all cases are due to food and at times to drug and bacterial allergies. Also autodigestion by pancreatic enzymes rushed into the colon by hyperperistalsis may enlarge those ulcers and produce denudation of mucosa, perforation, bleeding or gross hemorrhage.

When resistance to infection is low, infection of the mucosa, fever, abscesses, fistulas, perforation and peritonitis may occur. When resistance is high, the allergic colitis can continue in varying degrees with no complications or fever due to infection.

3. Chronic allergy can produce scar tissue. This is evidenced especially in the permanent scarring of the corneas from recurrent corneal ulcers with persistent inflammation due to food allergy observed by this writer. Thus, allergy with or without secondary infection may cause irreversible fibrosis, narrowing or stricture in the colon.

4. Remissions can be explained by the tendency for clinical allergy to cease or decrease without apparent cause. Refractoriness to the allergic reaction after a severe allergic attack of asthma or allergic headache or chronic ulcerative colitis is best explained by the exhaustion of specific reacting bodies in the shock tissues or temporary failure of production of such bodies. Thus even though causative allergens of foods or inhalants are ingested or inhaled, the allergic manifestation is minimal or absent.

The decrease or absence of food allergy during the summer months, long reported by this writer,[21] can explain temporary remissions in some

food-sensitive patients. And the decrease or absence of symptoms in the seasons, especially the winter when the allergenic pollens are out of the air, causes partial or complete relief from chronic ulcerative colitis due to pollen allergy. Temporary or intermittent ingestion or inhalation of allergic substances, moreover, can explain irregular exaggerations of ulcerative colitis.

5. Localization of this disease in the rectum or other parts of the colon is better explained by allergy than by infection. The spreading tendency of atopic dermatitis is well known and probably exists in the allergic colon, explaining the extension of chronic ulcerative colitis in many patients.

6. Fever may be due to food allergy alone.[19] Usually a secondary infection is responsible.

Thus allergy must receive adequate and experienced study as the probable major cause of all cases of this disease. The colon may be the only shock organ of allergy, though manifestations of allergy in other tissues may exist. Carefully taken dietary histories may reveal dislikes or disagreements to foods, especially to milk. Such histories may or may not indicate clinical allergy. Negative histories, moreover, do not rule out food sensitization. As in most chronic food allergy, skin reactions to allergenic foods are rarely positive, emphasizing the necessity of diet trial for the study of such sensitization. Inhalant allergy should be suspected when its other manifestations are present, and when definite positive skin reactions are obtained. The colon may be the only shock tissue of pollen allergy. The occurrence of inhalant allergy without skin reactions in about 10 to 15 per cent of all inhalant-sensitive individuals also must be remembered.

TREATMENT

Our treatment, therefore, considers allergy in all patients in the following manner:

1. For the study of possible food allergy in mild or moderate cases the writer's fruit and cereal-free elimination diet[16] is preferred. Lamb usually is the only allowed meat. Possible allergy to beef when sensitization to milk is present or assumed must be suspected. Ample amounts of food in the menus are necessary. The patient should be weighed every two days. More of the starch, sugar and, to a lesser extent, fat in the diet should be taken by the patient if weight lessens. Trays should not be removed until most or all the served food has been ingested. Protein can be increased up to 75 to 120 grams a day by giving one to five cans of Gerber's or Swift's strained lamb daily, especially if hypoproteinemia is present. The included vegetables may be pureed, but when allergy is brought under control, this may not be necessary. In the initial studies the vegetables can be eliminated entirely, especially if improvement does not occur in seven to ten days. Calcium carbonate, 2 grams, and ascorbic acid, 50 mg. a day, are advisable.

Improvement usually is apparent in three to fourteen days. When assured, rice, rye and corn can be added, giving one daily for five to seven

days before trying another. Later egg, wheat and other individual vegetables and cooked fruits gradually may be added. Since milk is the most common cause of colonic allergy it should be omitted for weeks or even months. This is especially important if a distaste or disagreement for milk has occurred at times for years. With ample protein in meat, calories in sugar, starches and fats in the diet and the prescribed calcium, milk can be excluded for months or years without nutritional deficiency. If symptoms recur the recently added foods must be excluded.

The prolonged exacerbations of ulcerative colitis (see Case 3) in some patients, arising from allergenic foods ordered by this writer or eaten against orders, together with the associated resultant infection, bleeding and anemia which may arise, deter further trial of such foods in well-controlled patients. Thus such allergenic foods, especially milk, have been eliminated entirely from the diets of many of the writer's patients for several years (see case reports), and no nutritional impairment has resulted.

If improvement does not occur in two weeks, and food allergy is definitely suspected, a minimal elimination diet of lamb, white potato, sugar, tapioca, noniodized salt and water can be ordered. In order to maintain nutrition and weight, feedings of this diet may be given four to six times a day. Along with lamb chops, roast and minced lamb, a can of the strained lamb three to six times a day can be given. Thus this minimal diet readily contains from 70 to 120 grams of protein and 2,000 or more calories each day. Vitamin therapy is discussed below.

In fulminating cases, especially with nausea and anorexia, the following formula[14] can be given every two and one-half to three hours throughout the day. Because of the frequency of milk allergy, beef is not allowed until symptoms are well controlled. Diarrhea and also fever have recurred with its use in a few patients.

Strained Meat Liquid Formula for Chronic Ulcerative Colitis (Rowe)

Gerber's or Swift's strained lamb	8 cans or 800 gm.
Soy oil	53 c.c.
Sugar, cane	170 gm.
Potato starch	30 gm.
Salt	2 tsp. or 8 gm.
Calcium carbonate	½ tsp. or 2 gm.
Water	qs. 2000 c.c.

Protein, 128 gm. Calories, 2000

Cook the starch, salt and sugar in 1 cup of water for 10 minutes. Then add the meat and oil, and cook with low heat for 10 to 15 minutes. Reduce the amount of starch to yield a thinner product.

Along with this formula, white potato, tapioca or arrowroot cooked with sugar, caramel and salt, white potato as such, lamb, water and salt may be given three to four times a day. This formula may be fed by nasal intubation in 200 to 300 c.c. amounts every three to four hours if nausea is persistent and anorexia is marked. With definite improvement other foods may be added as suggested above.

POLLEN AND OTHER INHALANT ALLERGY

2. When pollen and other inhalant allergy is indicated by history or skin tests, desensitization, as recently advised by the writer, and strict environmental control, including a pollen filter in the window, are indicated. Pollen, dust and other inhalant allergy should also receive thorough study in patients suspected of food allergy if diet trial does not produce results in two to four weeks. As in atopic dermatitis due to pollen and other inhalants, desensitization[16] is necessary with multiple antigens in dilutions weak enough to produce gradual improvement and no exaggeration of symptoms. Coseasonal therapy especially requires a careful and often slow increase of very dilute antigens. With definite improvement, stronger dilutions gradually can be injected. Desensitization must be perennial, and continued in such pollen-sensitive patients for at least two years and usually for longer periods.

3. Vitamin therapy is important. Vitamin C, 50 to 100 mg., daily, Drisdol and synthesized B complex vitamins by mouth are advisable. If avitaminosis is definite, then vitamins B and C may be given parenterally. Allergy to vitamin C[19] may occur with sensitization to all or practically all fruits. Occasional allergy to thiamin and possibly to other vitamins in the B complex must be remembered (see Case 3). Crude liver extract intramuscularly may be more helpful than the above vitamins in relieving B vitamin deficiency. Moreover, it may produce a beneficial nonspecific action.

4. Transfusions and iron, if tolerated by mouth, are indicated for anemia.

5. For bleeding, transfusions, vitamin K, if indicated, and possibly rutin are advisable.

6. For hypoproteinemia, transfusions and irradiated plasma are indicated. The protein in the diet can be increased up to 150 gm. a day with the use of Swift's or Gerber's strained lamb, either as such or in the above formula. This decreases the necessity of amino acids by mouth and vein which are less efficiently utilized than are food proteins by mouth. Possibility of allergy to milk and pork allergens in trypsin-digested amino acids and their disagreeable taste, moreover, contraindicate their use in this disease. The good results with enzymatic casein digest and dextri-maltose reported by Machella[8] require the consideration of relief of causative food allergy.

7. Aspirin, codeine and at times tincture of opium are necessary for pain and cramping. Other antispasmodic drugs are disappointing, supporting Alvarez's opinion[1] that such drugs, including atropine, are relatively ineffectual in controlling spasm in the bowel. Some relief from cramping from antihistaminic drugs in some patients supports the allergic etiology.

8. Duodenal extract was not used to obtain our good results. In three patients it was distasteful, and caused nausea, anorexia or diarrhea.

9. Barbiturates for nervousness and sleep are justified. They should

be taken only when necessary and never in amounts productive of stupor or confusion. Allergy to them or the excipients may occur.

10. When secondary infection occurs or is probable, sulfadiazine by mouth may be valuable. Sulfaquanidine, sulfathalidine or sulfasuxidine in larger doses occasionally aid.

Svartz[21] and recently Bargen[4] have reported good or excellent results from a new preparation Salicylazosulfa pyridine (Salazopyrin). This has been confirmed in a few of our patients.

Allergy to all of these drugs may exist, or develop during their use, causing fever, nausea, cramping, increased diarrhea, skin eruptions and other symptoms.

11. In one of the writer's cases 1 gm. of streptomycin four times a day by mouth controlled persistent fever in two days. Aureomycin and Chloramphenicol (Chloromycetin) in .25 to .5 gram doses produced similar results. The dose should be reduced to .25 gm. three to five times a day as soon as fever has ceased. Allergy and especially toxic symptoms from these drugs must be anticipated. Aureomycin[10] seems preferable if tolerated because of its under antibacterial activity. When this is not tolerated, Chloramphenicol often is effective.

12. To increase resistance to infection, stock streptococcic, staphylococcic, Bargen bacilli or respiratory vaccines at times may be valuable. Benefit from an autogenous hemolytic staphylococcic vaccine has been reported. These vaccines should be started with dilutions of 1:10,000 to 1:1,000,000, anticipating possible allergic reactions thereto. Rapid increase through the 1:1,000 and 1:100 and 1:10 dilutions is justified every three to four days if local or general reactions and increase in the colitis do not develop. Abnormal susceptibility or allergy to such vaccines occurs in some patients, producing a local reaction suggestive of a possible Arthus type of reaction.

13. Reassurance of the patient, based on the good results obtained with the above therapy, is important and justified. Nervous disturbances in severe cases, we believe, are the result rather than the cause of this disease. As in other types of allergy, nervousness can activate a potential allergy in the colon. The production of the severe pathologic condition of chronic ulcerative colitis by psychosomatic causes is illogical in our opinion.

SURGERY

Ileostomy or colostomy should not be done without adequate treatment based primarily on the probability that food and/or inhalant allergies are the major causes of an eczematous-like reaction in the colon. With elimination diets as here advised, nutrition and weight can be maintained and gradually increased for many weeks while these food and inhalant allergies are being studied and treated, and complicating infection, hypoproteinemia and anemia are being controlled. Only when perforation and peritonitis threaten, or when perianal abscesses and infection with fever increase in spite of this adequate treatment, is surgery justifiable. At present the

lowered mortality from ileostomy due to antibiotics, together with the prevalent uncertainty about the cause of this disease, is responsible for "early ileostomies" in many patients with chronic ulcerative colitis which, in our opinion, could be controlled as here advised. Subsequent complete colectomy, usually in two stages, with its possible mortality and complications, is usually necessary after ileostomy for good results. Today's minimal mortality of approximately 5 to 12 per cent from these three operations, together with the life-long handicap of an ileostomy contraindicates such surgery if medical treatment can control the disease. Until the entire colon, including the anus, is removed, these allergic tissues in many patients will be painful, inflamed, yielding mucus, blood and serous fluid and be susceptible to secondary infections with resultant fever, abscesses and fistulas as long as the causative food and/or inhalant allergies are uncontrolled. Such surgery in our opinion removes the shock organ of allergy, which is impossible in any other manifestation.

With our plan of treatment, fever, diarrhea and bleeding may continue for three to six weeks or even for longer periods with later recovery. The recent use of Aureomycin, Chloramphenicol and Salazopyrin by mouth has controlled infection in some patients, helping to obtain better results with the control of the allergies. If nutrition is being maintained as above advised, and if possible secondary infection and anemia are treated as above described, then prolonged treatment based on food and inhalant allergy as the major causes is highly justifiable. Especially in moderate and uncomplicated cases, surgical treatment is not justifiable. Recovery, moreover, has occurred in a number of our very severe cases in which ileostomy previously had been advised. We confirm Bargen's[5] observation that a contracted, fibrotic colon will function well if the causes of the disease become quiescent or controlled. Boeckus holds that such shortened contracted colons at times may be the result of a spasm and edema rather than an irreversible fibrosis. The surgical drainage of perianal or recent fistulas, of course, is most necessary. More extensive palliative surgery around the anus and especially the removal of hemorrhoids in these patients is unwise because of the reduced resistance of tissues arising from infection and especially from localized allergy. The delayed healing of wounds[12] in certain patients with gastrointestinal allergy is of interest. Exaggeration of symptoms or fulminating activation of potential or quiescent chronic ulcerative colitis at times after proctoscopy and especially after sigmoidoscopy contraindicates them except for necessary diagnosis. Forceful proctoscopy especially with anesthesia is unwise. Auer's[3] report of the onset or an activation of severe allergic inflammation after injury of potentially allergic tissue may explain these bad results from proctoscopy. Injury to the mucosa, moreover, predisposes to abscesses and fistulas in patients whose resistance to secondary infection is impaired.

DISCUSSION OF RESULTS

The results of the writer's therapy, the complicating infections, the

TABLE I. CHRONIC ULCERATIVE COLITIS IN 101 CASES STUDIED IN THE LAST ELEVEN YEARS

Hospital Cases: 75 Office Cases: 26 Total: 101

Major Causes in Co-operating Patients (determined by results)
- Food allergy ..... 54 cases
- Food and pollen allergy ..... 4 cases
- Pollen allergy alone ..... 1 case

59 cases

(In 29 of these 59 cases obtaining good or excellent results, no sulfonamides or antibiotics were used.)

Probable Major Causes in Patients Whose Time of Co-operation was Limited
- Food allergy ..... 14 cases
- Food and pollen and other inhalant allergies ..... 7 cases

21 cases

Patients Under Present Treatment
- Probable allergy to foods and/or pollens and inhalants .. 6 cases

Poor Co-operation Occurred in ..... 5 cases
(No co-operation in 15 cases, not included in this article.)

Failure from Antiallergic and Medical Treatment ..... 4 cases

OPERATIONS

In five of the above patients previously controlled by antiallergic and medical treatment, ileostomy and later colectomy were done because of severe exacerbations. In our opinion these recurrences were due to breaks in the diet and/or uncontrolled pollen allergy in four patients. Complicating exacerbated infection was responsible in one patient. Ileostomy and colectomy were done in three patients with probable allergic colitis, but in whom we found co-operation was inadequate.

In three other patients who received no antiallergic treatment, ileostomy was done, with two deaths.

DEATHS

In addition to the above two deaths, fatalities occurred in three cases from peritonitis during the first week or two of antiallergic and medical treatment. Death from peritonitis occurred in four patients previously controlled with our treatment. Ileostomy and/or colectomy were done in three of these patients. These deaths from peritonitis occurred before penicillin was available or when its use was restricted, or before streptomycin, Aureomycin, Chloramphenicol and Salazopyrin were discovered.

operations and deaths occurring in all patients studied in the last twelve years are summarized in Table I. As the study has progressed, it has become increasingly evident that good results demand an understanding by the doctor and the patient of the characteristics of clinical atopic allergy and its response to indicated treatment. All physicians treating chronic ulcerative colitis should study these characteristics, progress and response to the treatment of food and inhalant allergies in many cases, especially of atopic eczema or dermatitis, a replica of which in the writer's and Andresen's opinions is the major and underlying pathologic process in chronic ulcerative colitis. The physician moreover must gradually establish a philosophy in the patient which assures unswerving continued co-operation and accepts accurate diet trial and later prolonged elimination of probable or definitely allergenic foods, which justifies eating for health and maintenance of nutrition rather than pleasure alone, and which in inhalant-sensitive patients accepts the careful and necessarily prolonged desensitization therapy and the use of pollen and dust filters and environmental control when indicated. This necessary and restraining philosophy is a small requirement compared with the lifelong handicap and inconvenience of an ileostomy and the usually required total colectomy as the other alternative.

With the realization of the above and the better control of secondary infections with aureomycin, chloromycetin and streptomycin along with penicillin and the sulfonamide drugs, our results in co-operative patients during the last two and a half years have greatly improved, as compared

with those obtained in the first years of our study and treatment. Up to nine years ago the possibility of pollen and other inhalant allergy often associated with food allergy as a cause of chronic ulcerative colitis was not realized. Since then, its importance gradually has become apparent, as will be reported in a forthcoming article. And the greater frequency of food allergy has been increasingly confirmed. Evidencing this improvement from our treatment is the occurrence of no death, ileostomy or colectomy in any patient who has continued to give full co-operation to the writer during these last two and a half years. But the understanding of the allergic cause and necessary treatment and the accepting co-operating philosophy may not be obtainable, justifying in such unfortunate patients the removal of the shock organ of allergy, the colon, which is impossible in any other manifestation of atopic allergy. This radical operation must be done, hoping that the occasional later establishment of the small intestine as a similar shock organ of allergy, with the development of regional and usually progressive enteritis, will not occur.

With the above comments in mind, the writer presents his statistics on all the patients with chronic ulcerative colitis studied during the last twelve years.

In our opinion our results indicate allergy as the major cause in fifty-nine patients in whom co-operation was satisfactory and in another twenty-one patients even though the time of their co-operation was limited.

Of the fifty-nine patients, thirty-eight have continued to co-operate for an average of three and one-fourth years, varying from one-half to eight years. Co-operation in another eleven patients continued for an average of one and one-half years, varying from one-fourth to two years; their present control is not known. Good or excellent control occurred in ten other patients for an average of two and four-fifth years, varying one-half to eight years. Recurrences in these ten patients, in our opinion, were due to breaks in diet in five cases. In two of these, ileostomy and colectomy produced good results. These operations were advised by other physicians and do not exclude the possibility that continued treatment based on the evident allergy with the present control of secondary infections would have yielded good results. Ileostomy, complicated later with perianal abscesses and peritonitis, resulted in death in one patient previously controlled by our treatment for eighteen months. Ileostomy was successful in one patient for six months. Then death resulted two years ago from recurrent ischorectal abscess, peritonitis and ileal obstruction. One patient, controlled with an elimination diet for eight years, developed persistent bleeding and fever, relieved by the removal of a vascularized infected descending colon. The possibility of a complicating pollen allergy during the last two years was present, but co-operation in indicated treatment was not obtained.

The twenty-one patients whose co-operation was limited, but whose results in our opinion indicated food and inhalant allergies as the cause, were under treatment for an average of two and one-half months, varying from

two weeks to eight months. That allergy was the probable major cause was indicated by the rapid control of symptoms, including the diarrhea, blood and mucus in the stools, cramping pain and fever in varying combinations. Sulfa drugs and penicillin were not used in ten of these patients. Penicillin and/or sulfa drugs were used in ten and penicillin alone in one patient. Food allergy was probable in nineteen and questionable in two of these patients. Ileostomy and colectomy in three and ileostomy in one of these patients were done. In these four patients co-operation was insufficient to exclude the possibility of relief from our treatment.

The comments on the operations and deaths in Table I in this series of 101 patients are sufficient. As stated above, it is our opinion that with our present attitude toward treatment and the full use of our new and old antibiotics fewer operations and deaths would have occurred.

CASE REPORTS

Case 1.—In 1942[13] the writer reported the first record of seasonal chronic ulcerative colitis of eight years duration, relieved by pollen therapy.

The woman, aged forty-eight years, was first seen in the Allergy Clinic at the University of California Hospital in September, 1940. Watery or loose stools with blood and mucus, associated with moderate varying fever, weakness, malaise and dull cramping pains in the lower abdomen, had recurred each year since 1931 from July or August until late November or December. Proctoscopic examination in 1934 in this clinic and since then in the fall months had revealed a granular, hyperemic mucosa with many ulcerations and bleeding areas. In 1936 a vaccine from the stools of hemolytic bacillus coli, staphylococcus aureus and alpha hemolytic streptococcus was given subcutaneously. The lysate was applied to the rectal mucosa and a phage from the bacteria was given by mouth. No relief was obtained.

Sick headaches had long recurred with her periods. Mild hay fever had occurred from 1918 to 1923 in Chicago. Her dietary history was negative except for belching fresh eggs. Her family history was unknown.

Skin testing with all important food and inhalant allergens by the scratch and intradermal methods was negative except for 1-plus reactions to red top and curly-lock pollens. Negative reactions occurred to her allergenic fall pollens.

Since her relief reported in 1942 from pollen therapy, perennial desensitization has continued with a multiple pollen antigen with complete control of her former symptoms of chronic ulcerative colitis except for a few loose stools for a week or so in the spring of 1943 and the fall of 1946. No consideration of food allergy and no other medication of any type has been given during this eight-year period. As previously reported, her eosinophilic leukocytes when first seen were 22 per cent. In four months they were 6 per cent, and in three more months when the pollens were out of the air they were 1 per cent.

Case 2.—Mrs. W., aged thirty, was first seen in the Peralta Hospital, because of chronic ulcerative colitis in January, 1944. Since the fifth month of pregnancy five years previously, two to twenty liquid stools with frequent traces of blood had been passed each day. Lower abdominal soreness and nearly constant tenesmus and urgency with movements had necessitated immediate access to the bathroom. Slight fever had been present and marked physical weakness, irritability and nervousness had occurred. Her weight had fallen from 165 to 135 pounds.

There had been no previous gastrointestinal symptoms, except for varying degrees of constipation for many years. There was no history of any previous chronic or allergic disease.

Proctoscopic and roentgen ray studies of the colon on three occasions had confirmed the present diagnosis. In spite of treatment from several internists, relief had failed. Recently her disease had been attributed to a repressed abnormal sexual desire of late childhood!

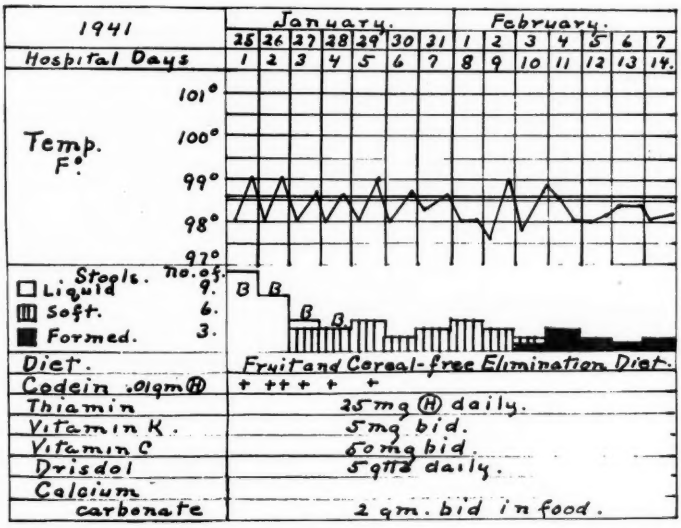

Fig. 1. *Case 2.* Mrs. F. W., aged thirty. Chronic perennial ulcerative colitis controlled with the fruit and cereal-free elimination diet without sulfonamides, penicillin or other drugs. The diarrhea, blood in the stools, cramping and slight fever gradually disappeared in the first ten days of the diet, and soft, less frequent stools appeared in three days. As in Case 3, this colitis developed during pregnancy. Excellent control for eight years has required the elimination of allergenic foods as noted in the case record.

Her dietary, drug and environmental histories revealed no indication of allergy. Likewise her family history was negative for allergic and chronic illnesses.

Her physical examination revealed a fairly well-nourished woman complaining of lower abdominal soreness, cramping and passing of numerous watery, bloody and mucoid stools. There was tenderness on pressure over the entire colon, especially in the lower left quadrant. Her blood pressure was 110/70. The rest of her examination was negative.

Laboratory Studies.—Urinalysis was negative. Hemoglobin was 73 per cent, leukocytes 9,400—polymorphonuclear cells 75 per cent, with 50 per cent segmented forms, lymphocytes 16 per cent, large mononuclear cells 7 per cent. Stools examined for ova and parasites were negative.

Roentgen ray study of her colon revealed marked shortening throughout with a tube-like, nonhaustrated appearance. Diffuse destruction of the mucosa was evident. Multiple constrictions were seen in the rectosigmoid and transverse areas, and to a lesser extent in the descending colon. The ileocecal valve was wide open and the terminal ileum was slightly distended.

Conclusion.—Extensive chronic ulcerative colitis of the entire colon.

Skin testing with all important food and inhalant allergens gave no reactions by the scratch method.

Treatment and Progress.—The writer's fruit and cereal-free elimination diet, vitamin C and calcium carbonate, as shown in Figure 1, were ordered. Vegetables

were pureed. Extra sugar was given in the form of cane syrup, in carbonate water and tea, in order to increase calories. Codeine was administered to relieve the severe abdominal cramping during the first few days.

Bowel movements reduced from eleven to four, and from liquid to soft in three days, and one to two formed movements were present after the tenth day. Abdominal soreness and cramping stopped on the sixth day, and her slight fever disappeared on the eleventh day.

In the last eight years there has been no return of diarrhea, bleeding, cramping or urgency with bowel movements. One or two formed daily stools or intermittent constipation have occurred. She had led a normal daily routine, doing her own house work, visiting friends and shopping, riding on horseback and in automobiles without fear of urgent bowel movements.

To maintain this control she has continued to eliminate all milk and its products, tomatoes, cabbage, cauliflower, eggplant, citrus fruits and spices. She has limited her intake of eggs and wheat.

"My colitis is very well controlled, though with carelessness with diet evidences of it return. It never restricts my activity. I am happy to be doing all the things I wish, especially in the last six years. In the summer and fall months for the last three years we have gone to a horse show every weekend. I can ride 10 to 20 miles a day without symptoms and without fatigue the next day. My present weight is 142 pounds."

Comment.—The rapid relief of this diarrhea with varying amounts of blood and mucus and the daily cramping, tenesmus and bowel urgency, and her return to normal family and social routine without fear of sudden bowel movements depended entirely on the prescribed elimination diet. As in twenty-eight other patients obtaining good results in this series, no sulfa drugs or antibiotics were given.

In this patient the colon was the only shock organ of allergy. The dietary history, as so often occurs, revealed no dislikes or idiosyncrasies for any foods suggestive of possible allergy. The skin reactions were negative as was the family history for allergy. Constipation, as in Case 3, for a number of years was the only preceding gastrointestinal symptom.

During the last five years slight indications of her former colitis have occurred for only a day or two when small amounts of milk and other foods listed above have been eaten against orders. She has led a normal, vigorous and happy life, realizing the necessity of adhering to her elimination diet.

Case 3.—A woman, S. S., of thirty-nine years, was first seen in the University of California Hospital in October, 1945, because of chronic ulcerative colitis. Diarrhea had developed in the seventh week of her third pregnancy three years previously. Mucous colitis was diagnosed, but diet and medications were ineffectual. Since then, seven to eight soft or liquid stools had been present practically every day. In January, 1944, treatment in the hospital gave no relief. Stool examinations for parasites and pathogenic bacteria were negative. During these three years stools had become more watery, foul and bloody. Great urgency had been present all the time, requiring constant proximity to the bathroom. Because of economic necessity she had done some housework every day, even though moderate weakness and a loss of 10 pounds had occurred. Diet, medicines and other treatments had failed. Moderate fever had occurred at intervals and had been present for the last two weeks.

Except for constipation throughout her life, no other symptoms or illnesses had ever occurred before this illness.

Her dietary history revealed no dislikes or idiosyncrasies for any foods.

Her environmental and drug histories revealed no indication of possible allergy.

Her family history also was negative for chronic disease and allergy.

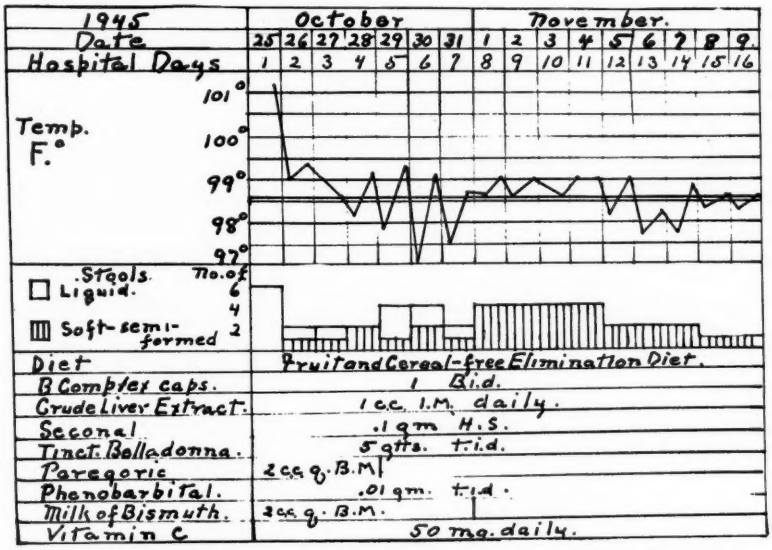

Fig. 2. *Case 3.* Mrs. S. S., aged thirty-nine. Chronic perennial ulcerative colitis controlled by the fruit-free elimination diet. The diarrhea was reduced in one day and to one to two soft stools in twelve to sixteen days. Fever disappeared in thirteen days. No sulfonamides or antibiotics were used. The value of the liver extract and phenobarbital is questionable. In the last three and one-half years two moderate exacerbations due to breaks in the elimination diet have occurred.

Her physical examination revealed a slender, worn appearing, but composed woman, with a temperature of 101° F. Her examination was negative except for moderate diffuse abdominal tenderness and a tender inflamed anus.

Laboratory Studies.—Urinalysis was negative. Blood count (October 25) showed hemoglobin 90 per cent, erythrocytes 4,700,000, leukocytes 8,800; differential count showed polymorphonuclear cells 41 per cent, with 30 per cent segmented forms, lymphocytes 43 per cent, eosinophiles 16 per cent. On November 5 hemoglobin was 88 per cent, erythrocytes 4,700,000, leukocytes 8,700; the differential count showed polymorphonuclear cells 73 per cent, with 62 per cent segmented forms, lymphocytes 14 per cent, eosinophiles 14 per cent. Three stool examinations and cultures were negative for bacilli in the typhoid, paratyphoid and dysentery groups. Four stool examinations showed no parasites or ova. Serum protein: albumin 3.2 gm. per cent, globulin 3.9 gm. per cent.

Proctoscopic examination up to 13 cm. showed a granular appearing, erythematous, easily bleeding mucosa. Roentgen ray study of the colon showed a rapid passage of barium throughout the colon which was narrow and rigid. The barium passed into the terminal ileum with little pressure. The borders of the terminal ileum were smooth and rigid. Haustrations in the colon were absent except in a small portion of the ascending colon, and the borders were smooth throughout. Opinion: Chronic ulcerative colitis, probably involving the terminal ileum.

Treatment and Progress.—The writer's cereal and fruit-free elimination diet with other medications shown in the chart were ordered. Fever decreased in the first six days. Soft infrequent stools immediately developed, except for two or three watery stools on the fifth to the seventh days. In one week urgency was less frequent. On discharge on the sixteenth day her fever was absent, urgency had disappeared, and one formed daily stool was being passed (Fig. 2).

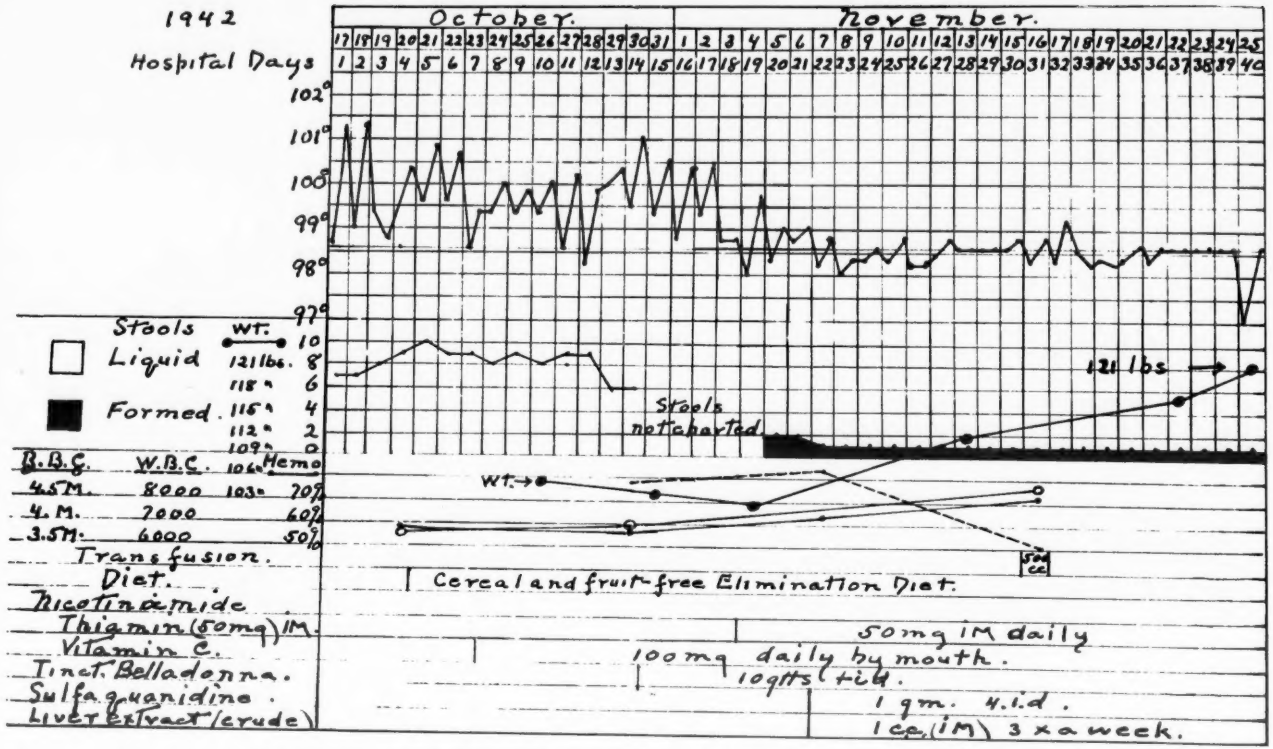

Fig. 3. *Case 4.* Mrs. A. B., aged thirty-five. This severe recurrent nonseasonal chronic ulcerative colitis was controlled in fourteen days on the fruit and cereal-free elimination diet. No sulfonamide or liver extract was given until control of colitis had occurred. As in Case 5, excellent gain in weight resulted with the control of the colitis on this diet, showing that milk and egg are not required, providing the prescribed diet contains adequate calories, protein and vitamins. During the last six and one-half years, there have been three moderate exacerbations of her colitis due to breaks in the diet.

In two months strength and appetite had increased and two or three formed stools were occurring daily. In four months there were two to three semi-formed, soft daily stools with no blood or mucus. No gas, cramping or any gastrointestinal distress was present.

During the summer and fall of 1946 all symptoms were controlled. She passed zero to three semi-formed or formed stools daily. Her weight was 100 pounds. B complex capsules daily for one week resulted in diarrhea, and when taken a few weeks later again caused immediate diarrhea.

In December after she had eaten white bread without permission for four days, loose stools developed and increased to eight or nine a day four days later. Soreness and cramping in the right abdomen persisted for twelve days; fever arose up to 100° F. and continued for about six weeks. Five to ten soft to loose bowel movements were passed each day and traces of blood were present in the stools. In mid-February these symptoms gradually disappeared. In two months her weight had increased to 97 pounds. Her appetite was "wonderful," and she felt better than at any previous time in her life. During the fall of 1947 she traveled through the Midwest and occasionally broke her diet. Moderate diarrhea with traces of blood, slight fever and loss of weight resulted. With strict adherence to the diet these symptoms disappeared in two or three weeks.

During the last two years she has adhered to her diet at all times. Her colitis has been well controlled. She has done all of her own work.

Comment. The relief of the long standing diarrhea, cramping, urgency and intermittent fever in two weeks, with continued control in the last four years, has depended on strict adherence to the fruit and cereal-free elimination diet. Only two moderate exacerbations have occurred, both due to breaks in the prescribed diet. In the last two years all of her symptoms have been continuously controlled due to strict adherence to the diet, and no medications of any type have been given. Her health and strength and weight have been normal.

This ulcerative colitis started quite suddenly, as occurs not infrequently in this disease. Constipation present since childhood, as in Case 2, was her only preceding symptom or illness. The absence of a history of dislikes or disagreements for any foods shows that such a history is not necessarily present when allergy to specific foods exists.

Case 4.—A colored woman, aged thirty-five years, Mrs. B., was first seen in the Alameda County Hospital in October, 1942, because of chronic ulcerative colitis. In the preceding one and a half years exaggerated symptoms had been present on three occasions, producing fifteen to twenty-five watery movements, associated with varying amounts of blood and mucus, persistent fever and vomiting two or three times on many days, each attack lasting four to five weeks. Marked weakness, abdominal soreness, tenesmus and cramping and the loss of 15 to 20 pounds had occurred. Between the attacks three to four soft or liquid movements with some mucus had been present each day. The present attack had occurred for four weeks before entrance to the hospital. There was no previous history of gastrointestinal symptoms, chronic or allergic disease.

Her dietary history revealed no dislike or disagreement for foods, though milk "soured" in her stomach during the attacks. Her drug and environmental histories revealed no suggestion of allergy.

Family history revealed severe bronchial asthma in a sister. Her physical examination was negative except for diffuse soreness on palpation over the lower abdomen.

Laboratory Studies.—Her blood count is shown on the chart. Differential count October 17 showed polymorphonuclears 62 per cent, with 26 per cent segmented

forms, lymphocytes 29 per cent, large monocytes 16 per cent, eosinophiles 3 per cent, Wassermann reaction negative. Stomach analysis was normal, plasma proteins (November 19) were 6.5 gm. per cent. Three stool examinations for ova and parasites were negative.

Barium enema revealed absence of normal haustrations throughout the entire colon, especially marked in the descending portion. Conclusion: chronic ulcerative colitis with probable involvement of the terminal ileum.

Proctoscopic examination showed a pale, edematous mucosa with no visable ulcerations.

Treatment and Progress.—With the writer's fruit-free elimination diet, containing a small amount of the prescribed pureed vegetables, decrease in cramping, abdominal soreness and the number of stools occurred in one week, and formed stools were passed in twelve days.

During the next three years her symptoms were well controlled with the continued elimination of milk, wheat and fruit from the diet. All vegetables were taken nonpureed. In July, 1945, she reported three to four watery bowel movements with some epigastric pain and recent vomiting. Cream and uncooked fruit had been taken at times for three previous months. With their elimination her colitis disappeared, and six months later she was well controlled except for one to two soft movements for one day every week or two.

In October, 1947, she reported satisfactory control of her colitis during the preceding year and one-half. One semiformed daily stool had been passed. Recently occasional slight lower abdominal pain had occurred before a movement. Slight errors in the diet had been made, including some milk in cooking and the occasional eating of white bread and tomato. For two or three months she had been fatigued. With the resumption of the strict diet her fatigue and abdominal distress disappeared at the end of one month's time. Ferrous sulfate, 3 grains, three times daily was ordered because of a hemoglobin of 66 per cent. Because of a metabolic rate of minus 16 per cent, ½ grain of thyroid was ordered.

During the last two years and a half her colitis was well controlled until eight months ago. Then for three months abdominal soreness, occasional soft or liquid stools and weakness and nervousness had been present. During the preceding months constant breaks in the diet had been made. With the resumption of her fruit-free elimination diet her symptoms were controlled at the end of two weeks.

Comment.—The rapid control of the diarrhea and the blood, mucus, cramping, tenesmus and fever with the sole use of the fruit and cereal-free elimination diet, as shown in Figure 3, favors food allergy as the cause of this chronic ulcerative colitis. This is confirmed by the continued relief except for moderate symptoms when milk and other forbidden foods had been taken for varying periods in 1945, 1947 and 1948. With the resumption of the strict diet, rapid control of the resultant symptoms have occurred on each occasion. During these last seven years her colitis has not required even a brief hospital residence.

As in Case 1, no sulfa drugs or antibiotics were given while the fever and diarrhea were being controlled. Liver extract and sulfa quanidine were given in the last eighteen hospital days, but in the writer's opinion they were unnecessary.

The gain of weight of 14 pounds in twenty days shows that milk, egg and cereals are not required to increase weight when the allergic causes of chronic ulcerative colitis are controlled. Calories up to 2500 or more and protein up to 100 grams or more each day are readily available even with the minimal elimination diets, especially when the strained meats of Gerber or Swift are utilized.

Case 5.—A woman, Mrs. G., aged thirty years, was first seen in the San Francisco County Hospital in February, 1946, because of chronic ulcerative colitis.

Eight months previously two to three loose daily bowel movements had devel-

oped. During the next two months a gradual increase to ten or twelve watery movements, associated with chills, fever, soreness in the abdomen, cramping and tenesmus and a loss of 20 pounds, occurred. In late August she was hospitalized, and with a milk-free, low residue diet, started after the twentieth day, her fever was reduced from 104° to 99° in thirty-five days. At that time occasional soft stools developed, and at the end of sixty days a normal temperature was present and two to three formed daily stools were passed. During her hospital stay three transfusions, B complex vitamins and antispasmodics were given. Sulfasuxidine, 5 grams, four times a day, was given for three weeks after September 8, and crude liver extract, 2 c.c. intramuscularly daily, was given for six weeks after September 8.

After discharge from the hospital on October 31, milk was added to the diet, and during the next month a normal diet was resumed. Within one month mucus and blood recurred, and in two months she was passing ten to twelve liquid bowel movements, with much soreness and pain in the anus, marked tenesmus, daily fever and a rapid loss of weight.

There was no previous history of any gastrointestinal or chronic illness before the onset of her present colitis. Her family history revealed no predisposition to any chronic or allergic disease. Her dietary, drug and environmental histories revealed no suggestion of any allergy.

Because of the severe return of her ulcerative colitis since early December, she re-entered the hospital on January 30, 1946. Physical examination revealed a thin, moderately weak woman, weighing 89 pounds, with a temperature of 103° F. Her examination was negative except for moderate distention and soreness on pressure over the lower abdomen. Her blood pressure was 117/70. Sigmoidoscopy revealed an erythematous, granular mucosa which bled on the slightest pressure. Moderate sized ulcers, covered with a purulent exudate, were present in the rectum and sigmoid.

X-ray of the colon revealed a shaggy, saw-tooth outline from the cecum to the lower sigmoid. Marked thickening of the walls was present in the transverse colon. Almost a complete loss of normal mucosal pattern was seen from the mid transverse to the rectum. Compared with the findings during her previous entrance, there was a progressive narrowing of the lumen and loss of haustrations of the colon. Conclusion: Severe chronic ulcerative colitis.

Laboratory Studies.—Her blood counts are shown in Figure 4. Differential count showed polymorphonuclear cells 70 per cent, with 50 per cent segmented forms, lymphocytes 17 per cent, large mononuclear cells 6 per cent. Urinalysis, Kolmer and Kline tests were negative. More stool cultures showed no bacteria in the typhoid, paratyphoid A, B or dysentery groups. Intradermal tests with coccidiodin and brucellin were negative. Serum proteins: albumin 2 gm. per cent, globulin 2.9 gm. per cent.

Treatment and Progress.—During the first seven days the former low residue, milk-free diet and sulfasuccidine, crude liver extract intramuscularly, vitamins and antispasmodics were given with no reduction in her symptoms. Then the writer's fruit-free, cereal-free elimination diet was ordered, and with interval feedings over 2000 calories were ingested daily. The number of stools and fever gradually decreased, and in three weeks two to three formed stools were passed. Fever was markedly reduced and her appetite, strength and weight steadily increased.

Sigmoidoscopy at this time revealed no bleeding ulcers. The mucosa was less granular and edematous, though it still bled easily on swabbing.

During the following thirty days in the hospital there were one to three formed daily stools. Her blood count steadily increased, even though only one transfusion was administered during the seventy hospital days. Her fever fell to 99° F. in the fifth week. Her former irritability and "inward nervousness" disappeared, and her appetite and strength were normal on discharge. In spite of the elimination

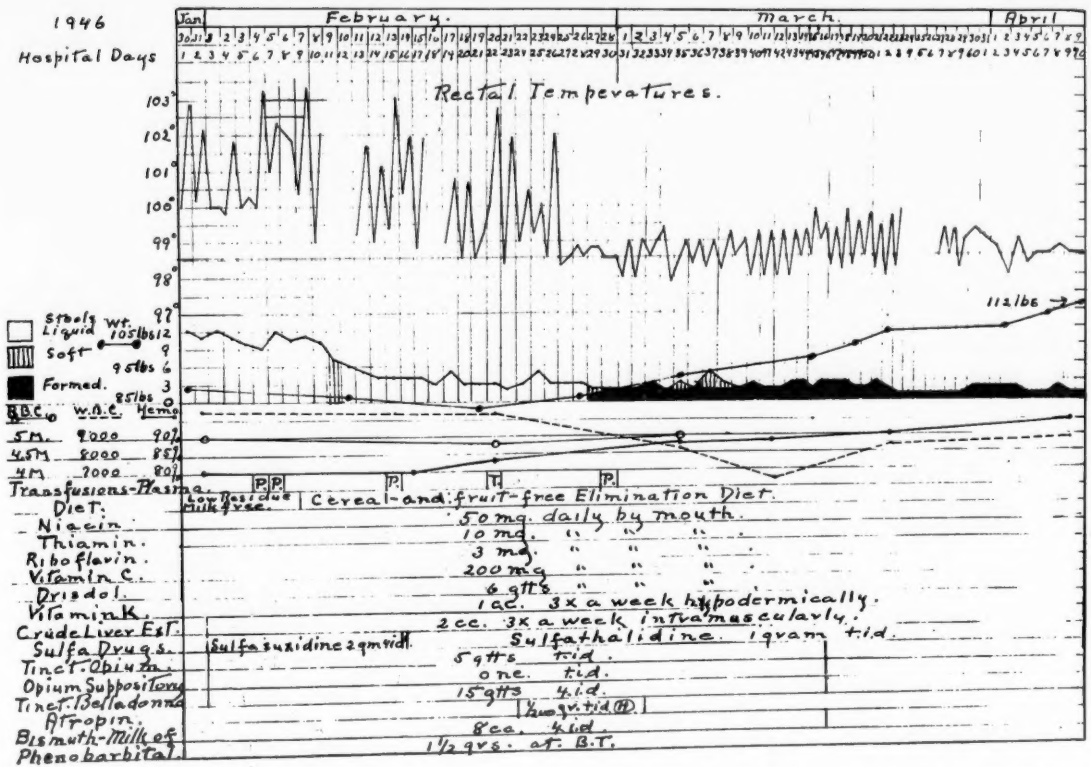

Fig. 4. *Case 5.* Mrs. R. G., aged thirty. This fulminating chronic ulcerative colitis was controlled with the fruit and cereal-free elimination diet. The benefit from the sulfonamides and the small dose of crude liver extract is uncertain. The necessity of all the sedatives and antispasmodics is questioned today. The steady gain in weight after the diarrhea and fever were reduced occurred with no change in the diet, and with no milk, egg or other common allergenic foods in the diet. The excellent control of this colitis in the last three years had depended on strict adherence to the diet and in the last one and one-half years on the control of pollen allergy, which is of probable secondary importance to this major food allergy.

diet from which milk, egg and other foods were entirely excluded, her weight had increased from a low of 84 pounds to 117 pounds.

During the last nearly four years her colitis has been under excellent control, except for a few days six months after I first saw her, when for a few days white bread and butter had been taken. Moreover, on two other occasions she ate milk or wheat for one meal with resultant loose stools and cramping for two to three days afterwards. Otherwise, except for the results of probable pollen allergy discussed below, she has passed one to two formed stools a day and has been free of abdominal and rectal distress and soreness.

Because of two or three loose movements with some distention and cramping for a few days in August, 1946, and again four to six loose movements with traces of blood and fever of 101° for a period of two weeks in July, 1947, probable pollen allergy complicating her definite food sensitivity was assumed. During the last two years, desensitization treatment with a multiple antigen containing the spring, summer and fall pollens of her vicinity have been selfadministered in dilutions varying from 1:5,000 billion every three to four days up to the 1:5 billion dilution at the present time. During this last year and a half there has been no return of her colitis, no fever, and no abdominal distress or pain. About four months ago soreness in her right maxillary antrum with pain in her right forehead developed. Examination revealed a chronic maxillary sinusitis confirmed by x-ray findings. In spite of a radical Luc-Caldwell operation and delayed healing of her operative wound, her ulcerative colitis has been under perfect control, due to her adherence to her strict cereal-free and fruit-free elimination diet, plus rice, and extra vegetables, peaches and pears and her continued pollen treatment. Along with this, vitamin C, 50 mg. daily, and one B complex capsule have been given daily. Her present blood count is hemoglobin 85 per cent, erythrocytes 4,500,000 and leukocytes 11,000.

Comment. This control of the colitis during the last nearly four years has emphasized food allergy as the major cause with pollen allergy as a likely secondary factor. The sudden development of this localized allergy in the colon without previous illness often occurs in this disease. That the colon may be the only shock organ of allergy is evidenced in this patient. Her negative family history of allergy moreover is of interest.

The improved blood count, the change from frequent liquid bloody stools with cramping to the infrequent normal solid stools, the gradual reduction of fever, the excellent gain in weight even though milk, eggs and wheat were eliminated are shown in the chart. Since food allergy alone can produce fever, it is possible that the normal temperature (as in Case 4) would have developed without the use of the sulfathalidine. It is also uncertain how much the good results depended on the crude liver extract given intramuscularly three times a week. Without the control of food allergy this adjunctive therapy probably would have been useless. This excellent control during the nearly four years seems to have depended on her strict adherence to the diet and her perennial pollen therapy. This good control is emphasized by the failure of her recent sinusitis and Luc-Caldwell operation to activate her colitis in any way.

Her colitis remains controlled. No sulfonamides or antibiotics have been given in these nearly four years. There are two formed daily bowel movements with no cramping. Her diet excludes milk, wheat, corn, lettuce, citrus fruit, tomatoes, apricots, melons, bananas, spices and chocolate; and pollen therapy is being given by the patient under the writer's direction.

Case 6.—The following case record is included as illustrative of the second group of patients in Table I, where co-operation was limited but where results from the writer's treatment indicated food and/or pollen allergy as the probable major cause.

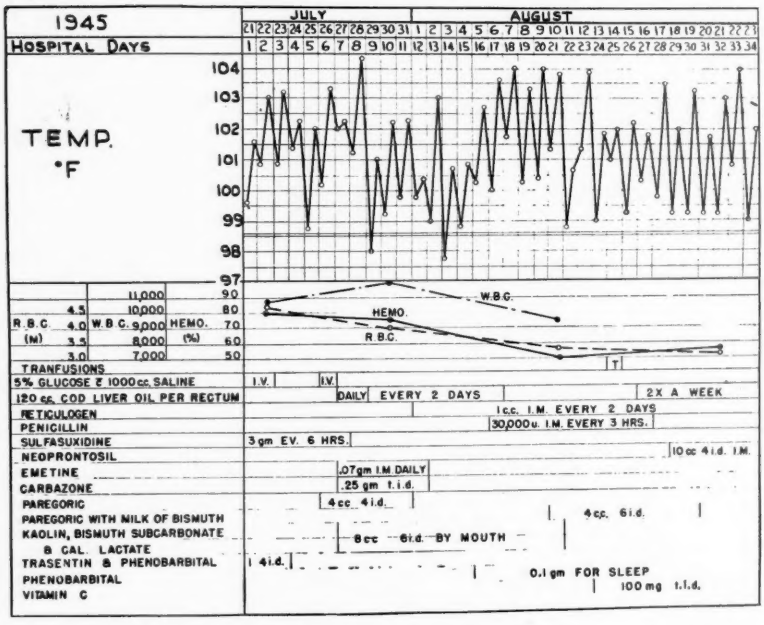

Fig. 5. *Case 6.* Mrs. R. C., aged twenty-six. Chronic ulcerative colitis treated with a high protein, high calorie, low residue diet, and liver extract and various drugs shown in the chart, with no results. Emetine, carbazone, sulfasuxidine and the limited amounts of available penicillin were not beneficial.

Recent follow ups have failed in fifteen of these twenty-one patients. Of the remaining six, symptoms have recurred in varying degrees and frequently in all of them, colonic surgery having been done in four of these patients. In our opinion continued treatment based on allergy as the major cause would have controlled these symptoms in most cases.

A young woman, Mrs. R. C., aged twenty-six years, was first seen at the University of California Hospital in September, 1945, because of chronic ulcerative colitis. For two years before the third month of her pregnancy one and one-half years ago, streaks of blood had been present in normal bowel movements on two or three occasions each week. This blood was absent during the last six months of pregnancy. It reappeared, however, two or three months postpartum for only one month.

On May 30, 1945, blood reappeared in her stools. They became more frequent, and in late June three to four semi-formed stools with some blood and mucus but with no pain were being passed in each twenty-four-hour period. While she was motoring from Chicago to San Francisco in early July, watery stools developed, increasing in number and frequency from every four to every one to two hours. Cramping, urgency and tenesmus with the movements and a persistent fever were present. She entered another hospital in San Francisco on July 21. In spite of the administration of liver extract, penicillin, sulfa drugs, emetin, carbazone and other therapy, as shown in Figure 5, her fever and many watery bowel movements continued. Her laboratory studies gave the following results: Urinalysis was negative. Her blood counts are shown in the chart; her differential count (July 22)

showed polymorphonuclear cells 90 per cent, with 52 per cent segmented forms, lymphocytes 23 per cent. Three stool examinations for ova and parasites were negative. Stool culture for bacteria in the typhoid, paratyphoid and dysentery groups was negative. Agglutination tests for typhoid and paratyphoid were negative.

Roentgen ray studies of the colon showed that haustrations were diminished in the descending colon and absent in the tube-like sigmoid. Small cylindrical areas of increased density in the transverse and descending colon and sigmoid suggested probable ulceration. Impression: early ulcerative colitis.

She was admitted to the University of California Hospital on August 24. There was no previous history of any gastrointestinal symptoms and no history of any clinical allergy or other chronic disease. Her periods had been normal. Her family history also was negative.

Her physical examination showed a weak, thin young woman with a fever of 102° and a pulse of 110. She was passing blood-tinged watery stools with a few blood clots and some mucus. Her abdomen was tender on pressure over the lower portion. No rigidity, organs or masses were felt.

Laboratory studies gave the following results. Urinalysis was negative. Blood counts are shown in Figure 6. Differential count (August 24) showed polymorphonuclear cells 79 per cent, with 67 per cent filamented forms, lymphocytes 24 per cent, large mononuclear cells 1 per cent. (Four differential counts done during her stay in the hospital gave similar results.) Kohlmer test was negative. Four stool examinations for parasites and ova were negative. Two stool cultures for bacilli in the dysentery, typhoid and paratyphoid groups were negative. All agglutination tests for typhoid, paratyphoid, tularemia and brucellosis were negative. Prothrombin time was 65 per cent of normal. Serum proteins: (September 11) albumin 2.3 gm. per cent, globulin 2.15 gm. per cent; (October 23) albumin 3.75 gm. per cent, globulin 2.65 gm. per cent.

Sigmoidoscopy with low spinal anesthesia showed a narrow rectum and sigmoid with multiple small polyps in the mucosa. There was a firm granulomatous ulcerated mass 3 by 4 cm. in size on the anterior rectal wall. The mucosa was erythematous and granular in appearance, and much bloody mucus was present.

Treatment and Progress.—The same type of diet, liver injections and medications given in the first hospital along with B. vitamins by vein and four transfusions were administered during the first eighteen days at the University Hospital. The bloody stools increased in number. The fever persisted and finally she became incontinent, confused and depressed. A rectovaginal fistula developed. On the nineteenth day the writer's fruit-free elimination diet was started, and during the first week incontinence and delirium gradually decreased and the stools decreased in number. Some soft and a few formed stools were passed (Fig. 6). Seven days later thrombophlebitis developed in both legs, and a bilateral ligation of the femoral veins was done. Six days later a massive hemorrhage from the rectum occurred, requiring transfusions on two successive days.

In spite of the above complications her fever continued to decrease, and soft or formed stools up to eight in twenty-four hours with a decreasing content of blood were passed. Her strength gradually returned and her appetite improved. Abdominal pain and soreness disappeared by October 4, she was ambulatory October 16, and gained six pounds in the last fourteen days in the hospital.

During the first ten days at home she gained another 10 pounds and her stools reduced to five or six a day along with two or three slight additional discharges of mucus. She returned by train to Chicago two or three weeks thereafter. Another physician advised a soft bland diet. At that time, however, she reported a further gain in weight and ability to do some of her housework and shopping, before the soft regular diet was taken.

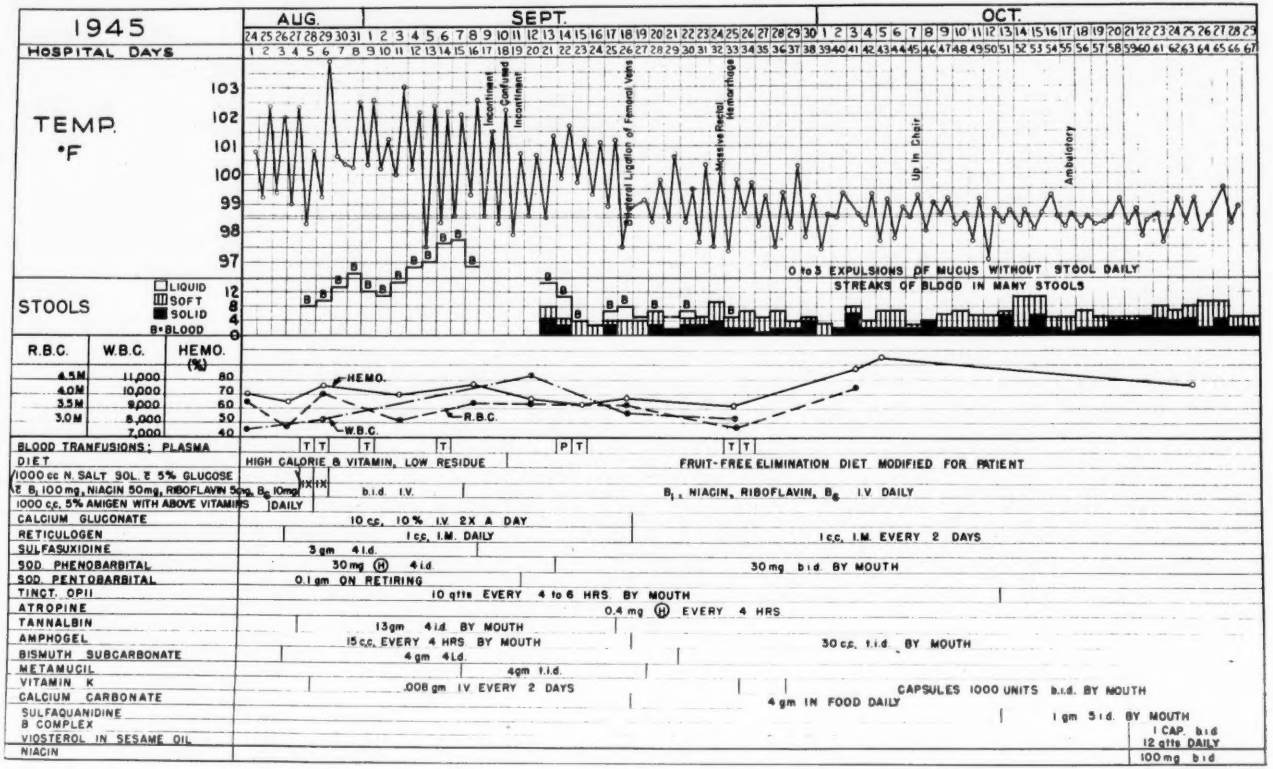

Fig. 6. *Case 6.* Mrs. R. C., aged twenty-six. With the same treatment and diet which had failed in the previous hospital (see Figure 5) diarrhea and blood increased, incontinence and confusion developed. Then with the modified fruit-free elimination diet, solid and soft stools developed in three days. Sulfasuxidine and all antidiarrheal and antispasmodic drugs were stopped except phenobarbital, tincture of opium, atropine and amphogel. Today these later drugs would have been stopped sooner or not prescribed. The steady improvement was not interrupted by the bilateral ligation of the femorals, and the large massive hemorrhage. The rapid and steady improvement with the elimination diet is in striking contrast to the lack of benefit with the usual nonresidue, high calorie diet and the many drugs ordered in the first hospital (Fig. 5) and during the first eighteen days in the second hospital.

July 11, 1946: A letter reported "wonderful health" until January, 1946. Then colitis recurred, requiring hospital care for six weeks. Streptomycin was given intramuscularly and later by mouth. Retention enemas of bismuth subgalante were administered twice a day, and a high calorie, high protein, high vitamin diet without the exclusion of any specific foods was prescribed. During the next two or three months she gradually recovered, and in the last two or three months her colitis was inactive and her weight was 125 pounds.

October 13, 1947: A letter reported the birth of a nine pound boy in July, 1947. Since her last letter there had been no recurrence of her colitis except for five to six watery stools each day during the fifth to seventh month of her pregnancy. Moreover during pregnancy her rectovaginal fistula discharged again and gradually ceased draining during the last month. She was comparatively well, doing some of her housework and caring for her two children. Her weight was 123 pounds.

January 13, 1948: A letter on this date stated that in December, 1947, her colitis was well controlled and a proctoscopy had revealed no ulcerations and an "almost normal bowel." Only rough foods were excluded from her diet.

On January 25, 1948, her stools increased from two soft movements to four or five in each twenty-four hours. Then her stools rapidly increased up to twenty liquid ones a day. She was placed in the hospital where streptomycin, penicillin, tincture of opium and other drugs were given without help for five weeks. An ileostomy was done and after six weeks she left the hospital having gained 15 pounds up to 126 pounds.

During the rest of 1948 she felt "tops," though the ileostomy was a "nuisance." She had eaten everything except roughage. "I still have two more operations if the colon again discharges blood, mucus and pus." No bleeding or discharge from the rectum had occurred, however, for several months.

Comment.—In our opinion the control of food allergy was responsible for the rapid relief of diarrhea, the gradual reduction of fever and blood in the stools and the gain in weight after this writer's treatment was initiated with a modified fruit-free elimination diet on the nineteenth day in the second hospital in 1945. This relief occurred even though the patient had been incontinent and confused during the preceding days and sulfasuxidine had been stopped. It continued and increased even though a bilateral ligation of the femoral veins was done and a massive hemorrhage occurred. During the next three months while this elimination diet was continued there was a gain of 16 pounds and a return of strength and energy.

Because of this excellent result it is our opinion that continued consideration of food allergy would have been wise. Individual foods should have been added gradually to the elimination diet, excluding any which re-established symptoms. The addition of cereal grains including wheat, egg, chocolate, and spices especially should have been delayed for weeks, and because of the great frequency of milk allergy in chronic ulcerative colitis it should have been eliminated for one or more years. It is generally recognized that milk is not necessary for the maintenance of nutrition and increase of weight, providing ample meat protein and calcium are included in the diet. This is exemplified by the increase of weight in other cases reported in this paper and especially by an increase of weight from 67 to 117 pounds in a young girl of fourteen years whose severe ulcerative colitis has been well controlled during the last year with a milk-free diet and pollen therapy, and by adequate gains in weight in many other patients who have had no milk for months or even years.

When symptoms recurred in this patient, the elimination diet which had yielded spectacular relief in 1945 and saved her from a recommended ileostomy while under this writer's care should have been resumed. With the bland general diet which was given, a recurrence of colitis recurred in two months, invaliding her for three

months thereafter. The relief which occurred for the next year can be explained by prolonged refractoriness to the causative food allergens which so often occurs in clinical allergy as already discussed in this paper. Then during the fifth to seventh month of her pregnancy, bloody, loose movements recurred, indicating a temporary reactivation of probable allergenic causes. Refractoriness continued for another seven or eight months after pregnancy terminated. Then a severe recurrence developed which failed to respond to a soft bland diet with milk and other treatment, because of which her present ileostomy was done. Thus during less than two and one-half years while her former bland, soft diet was eaten, there were two severe exacerbations and one moderate exacerbation of her ulcerative colitis.

It is our opinion that with the continued consideration of food allergy these exacerbations probably would have been prevented. During the exacerbations which did occur, the writer's elimination diet should have been resumed. Thus the ileostomy might have been prevented. This opinion is supported by many prolonged good results similar to those in Cases 2, 3 and 4 in this contribution.

This chronic ulcerative colitis developed in the early twenties with no previous history of gastrointestinal symptoms, no previous allergic manifestations and no familial predisposition to chronic or allergic disease. All of this in no way excludes the possibility of allergy as the underlying major cause of the chronic ulcerative colitis. Allergy in the colon may start as in other body tissues without any familial predisposition to allergy and the colon may be the only shock organ of allergy in the body. As is frequent, traces of blood had been in her stools on and off for three years, except for the last six months of her pregnancy, during which various manifestations of allergy as asthma or eczema may disappear, to reappear one or three months postpartum for varying periods of time.

SUMMARY

1. That an eczematous-like inflammatory reaction to food and less often to pollen and at times to other inhalant and drug allergies is the primary cause of chronic ulcerative colitis is indicated by the writer's study and treatment of this disease in the last twelve years.

2. When allergy is the sole cause, the symptoms gradually reduce or disappear with the control of the allergies.

3. When complicating infection, anemia, hypoproteinemia or avitaminosis are present, their treatment also is necessary.

4. Allergy best explains the primary lesions. Localized vascular allergy can cause the erythema, edema and a friable and easily bleeding mucosa. Granulation, erythema and oozing are also the main features of active atopic dermatitis. The herpetic ulcers can arise from minute vascular thromboses which also cause canker sores, the latter being due to food and at times to drug and bacterial allergies. With low resistance, secondary infection causes fever, fistulae, abscesses, perforation and peritonitis.

5. Remissions can be explained by the tendency to refractoriness to causative allergens or even to anergy which develops in clinical allergy, explaining recurrent asthma, allergic headaches or angioneurotic edema. The seasonal occurrence of symptoms due to pollen allergy and the decreased or absent symptoms in the summer months due to food allergy help to explain variations of symptoms.

6. The tendency for allergy to localize in specific tissues and to limited

areas of one tissue and the spreading tendency of atopic dermatitis can explain the localization and spreading characteristics of chronic ulcerative colitis.

7. Fever may arise from allergy, especially to foods or drugs, though complicating infection is the usual cause.

8. Treatment therefore should take food and pollen and to a lesser extent other inhalant and drug allergies into account in all cases of ulcerative colitis.

9. In mild cases the writer's fruit-free elimination diet and later on his minimal elimination diet usually control food allergies.

10. In fulmination cases the writer's strained meat liquid formula, containing 100 to 150 grams of protein and 2000 calories, together with additional lamb, potato, tapioca and sugar as tolerated, is advisable for the study of food allergy. Intubation of this formula is possible with nausea and severe anorexia.

11. Suspected pollen and inhalant allergies require strict environmental control, pollen and dust filters and desensitization with multiple antigens, as advised by the writer.

12. Complicating infections demand sulfa drugs and the new and older antibiotics, as indicated by the patient's response and tolerance to them. Aureomycin, Chloreomycetin® and Salazopyrin are of special help.

13. Anemia and bleeding require transfusions and iron if tolerated. Vitamin K and Rutin may be necessary.

14. Hypoproteinemia requires the advised high protein elimination diet, transfusions and human albumin.

15. Cramping, diarrhea and pain may require careful use of codeine and at times tincture of opium. Sedation is contraindicated, except at times with small doses of barbitals. Antispasmodics are disappointing and usually inadvisable.

16. Ileostomy with the usual total colectomy is contraindicated until adequate and experienced treatment based on probable food or inhalant allergy and possible drug allergy has been used for an adequate period as advised by the writer. When "early ileostomies" are done before such treatment is given, they are not justified in spite of the low mortality with antibiotics and present surgery.

18. Surgery should be reserved for those cases where perforation and peritonitis threaten life in spite of the vigorous use of the sulfa and antibiotic drugs or where uncontrolled perianal infection or abdominal abscesses or intestinal infection are continuing in spite of present therapy. Then, postoperatively, probable food, pollen or drug allergies must be adequately considered in treatment, particularly if any part of the colon, which is the shock organ of allergy in these patients, remains.

(References on Page 819)

TESTING FOR IDENTITY AND PURITY OF POLLEN EXTRACTS

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USERS of commercial pollen, who take the precaution to examine microscopically the batches as purchased, occasionally find them too badly contaminated for use, and sometimes even wrongly named. Though this condition has received little notice, its prevalence is indicated in the report by Ellis and Dahl (1947), which is possibly the only one in the literature. They state that, "By microscopic examination of 260 different lots of dry pollen purchased from commercial sources . . . 6.5 per cent was incorrectly labeled, and 5.4 per cent was seriously contaminated." The serious contaminations ran from 2 to 87 per cent of foreign pollens, and involved as many as eight different plant families in a single lot. Notice was taken of this condition by Veldee (1948) in recommending to collectors that batches of pollen be not contaminated with foreign pollens to a greater extent than 1 per cent, and that the collector or his immediate supervisor be well grounded in taxonomic botany.

It has been the experience of the writer that when excessive contaminations or misidentifications are brought to the attention of the collectors, they nearly always show themselves to be genuinely appreciative, and willingly replace the defective lots, so that it can be safely said that the defects are rarely, if ever, knowingly incurred, and it is to be hoped that some improvement will result from the application of Dr. Veldee's recommendations. This can best be advanced if consumers of commercial pollens carefully examine all lots of pollen, both microscopically and serologically, and reject those that do not conform to the recommendations.

Ellis and Dahl state that "the identification of a pollen extract is made with considerable difficulty, and the identification of contaminants in an extract, practically impossible." "The identification of pollen grains," they say, "is made with certainty and relative ease by a person properly trained." I find myself not in complete agreement with these statements. It is true that one can detect mislabeled and contaminated pollens by miscroscopic examination, providing the species under consideration have sufficiently distinctive morphological characters, but this is by no means always the case.

On the other hand, if the pollens are antigenically different, they may always be distinguished by their serological reactions. If they are antigenically identical, their distinction is not important.

In order to distinguish two pollen extracts, or to detect contamination of one with the other, it is necessary to procure two allergic sera with sensitizations to each of inverse dominance. It is not necessary that either be

From Lederle Laboratories Division, American Cyanamid Company.
Dr. Wodehouse is an Associate Fellow of the American College of Allergists.

TABLE I

Sites sensitized with		Tests with unknown extracts						Test with dominant allergen 1000 u.p. cc		
		1000 u.p. cc		2000 u.p. cc		2000 u.p. cc				
	w.	e.	w.	e.	w.	e.			w.	e.
Rod serum, Bermuda dominant	H	9	45	6	25	0		Bermuda	9	50
	J	10	50	7	15	0		Bermuda	0	
	K	10	45	7	30	0		Bermuda	0	
	L	10	50	6	30	0		Bermuda	0	
Jam serum, Timothy dominant	H	9	45	0				Timothy	0	
	J	9	50	0				Timothy	0	
	K	9	45	0				Timothy	6	30
	L	9	45	0				Timothy	0	

Reactions to pollen extracts of Bermuda, timothy and mixtures of the two (designated H, J, K, L) of sites sensitized with a Bermuda dominant and with a timothy dominant serum. After desensitization of the sites of each serum by H, J, K and L, they were tested with the allergens of their dominant sensitizations.

The fact that H had failed to neutralize the Bermuda sensitization, but had that of timothy, shows that it contains no Bermuda grass and is therefore pure timothy. Similarly K is shown to be pure Bermuda grass. Since J and L both neutralize the dominant sensitization of each serum they must both be mixtures of Bermuda grass and timothy. W indicates the diameter of the wheal and e that of the erythema; u.p. cc denotes Noon units per c.c.

the over-all dominant sensitization of its serum; thus, one serum often can serve in several identifications, if it possesses many sensitizations of varying degrees of dominance.

Bermuda grass and timothy were chosen to put this thesis to the test because their pollen grains are almost indistinguishable microscopically, and differentiating sera are readily available (1947). Four extracts were submitted for examination. They were Bermuda grass, timothy, Bermuda contaminated with timothy, and timothy contaminated with Bermuda. They were designated by letters (H, J, K, L) without revealing which was which.

Two sera* were chosen, one in which Bermuda grass was the sole dominant with no reciprocals, and the other in which timothy was dominant but reciprocal with orchard grass, perennial ryegrass, sweet vernal grass and redtop. Four sites were sensitized on one arm of a normal recipient with the Bermuda dominant serum, and four symmetrically opposite on the other arm, with the timothy dominant serum. The sensitizations were made by injecting intracutaneously 0.05 c.c. of the sera diluted 1:10. Twenty-four hours later the sites were tested with the unknown extracts, H, J, K and L, injecting 0.01 c.c. in appropriate dilution in the different sites (Table I). After the sites were completely desensitized to the unknown extracts, each was tested with the pollen of its dominant sensitization. Bermuda reacted only with the site that had been neutralized by H, and timothy only with that neutralized by K of their corresponding sensitizations, showing that H contains no Bermuda grass and that K contains no timothy, and since H neutralizes its timothy dominant site to timothy, and K neutralizes its Bermuda dominant site to Bermuda, H is identified as pure timothy, and K as pure Bermuda grass. The other two unknowns neutralize both

*The sensitization patterns of these sera have been reported (1948), designated as Jam and Rod sera.

the Bermuda and timothy dominant sites; hence they must be the impure samples containing both pollens.

It is often possible, when the contamination of an extract is slight, to tell which is the preponderant pollen. In this case the first reactions of J and L were both maximal with both sera and without significant differences. Nevertheless, they failed to neutralize their Bermuda dominant sites, so these were retested, and the retests show that J had come much closer to doing it than had L. Hence, it appears that J is the Bermuda contaminated with timothy and L is the timothy contaminated with Bermuda. After these conclusions had been reached, it was revealed that H was pure timothy, K was pure Bermuda, J was Bermuda with 3.5 per cent timothy, and L was timothy with 3.5 per cent Bermuda. The method is, therefore, capable of distinguishing the pollen of one grass from another and revealing contaminations of one with the other by as little as 3.5 per cent. In the case of the Bermuda grass, the identification is absolute because Bermuda grass is the sole dominant of its serum, with no reciprocals. But with the timothy, the identification is not so specific. It could as well be orchard grass, perennial ryegrass, sweet vernal grass or redtop, since these are reciprocal with timothy. However, it is doubtful if these grasses are antigenically distinct.

A similar experiment was done to see if it is possible to distinguish bur ragweed from sagebrush singly and as contaminations. Spri and White sera were chosen. The sensitization patterns of these have been reported elsewhere (Wodehouse, 1948, 1949). The dominant sensitization of Spri serum is to ragweed, with short, western and bur ragweeds reciprocal. Sagebrush is subordinate and reciprocal with marshelder, burweed, cocklebur and slender ragweed. It partly neutralizes the sensitizations to western, short and tall ragweeds but not appreciably that to bur ragweed. Hence, the latter was chosen for the experiment. The dominant sensitization of White serum is to Russian thistle, with sagebrush subdominant, being dominant to all sensitizations except Russian thistle and summer cypress. Bur ragweed sensitization of this serum is a weak subordinate, reacting only when both the serum and antigen are used in high concentration, as in the present experiment.

The experiment was done as before (Table II). Four sites were sensitized with the serum in which ragweed was dominant over sagebrush, diluted 1:10, and four with the serum in which sagebrush was dominant over the ragweed, diluted 1:4. Following neutralization of the sites by the unknowns designated as M, N, O, P, it was found that bur ragweed reacted only after neutralization with O, and sage brush only after neutralization with M. Hence, O is pure sagebrush, and M is pure ragweed; N and P are mixtures. Which is which, in this case, is revealed by the first reactions. P gives the larger reaction with the ragweed serum, and N gives the larger with the sagebrush serum. Hence, P is mostly ragweed and N is mostly sagebrush. After these conclusions had been reached, it was

TABLE II

Sites sensitized with		Tests with unknown extracts				Test with dominant allergen 1000 u.p. cc		
		1000 u.p. cc		2000 u.p. cc				
		w.	e.	w.	e.		w.	e.
Spri serum, Ragweed dominant	M	10	55	0		Bur ragweed	0	
	N	7	40	0		Bur ragweed	0	
	O	8	45	0		Bur ragweed	8	40
	P	10	40	0		Bur ragweed	0	
White serum, Sagebrush dominant	M	7	40	0		Sagebrush	6	20
	N	8	45	0		Sagebrush	0	
	O	9	45	0		Sagebrush	0	
	P	8	35	0		Sagebrush	0	

Reactions to pollen extracts of bur ragweed, sagebrush and mixtures of the two (designated as M, N, O, P) of sites sensitized with a serum in which ragweed was dominant over sagebrush, and one in which sagebrush was dominant over ragweed. After desensitization of the sites of each serum by M, N, O and P, they were tested with the allergens of their dominating sensitizations.

The fact that O failed to neutralize the ragweed sensitization, but did that of sagebrush shows that it is pure sagebrush. In the same way, M is shown to be pure ragweed. And since N and P both neutralize the dominating sensitization of each serum, they must contain both pollens.

revealed that O represented pure sagebrush, M was pure bur ragweed, P was bur ragweed with 3.5 per cent sagebrush, and N was sagebrush with 3.5 per cent ragweed. Owing to the reciprocal neutralizations of the ragweed serum the ragweed could as well have been short or western. However, it is extremely doubtful if any antigenic difference exists between these species. The sagebrush sensitization, on the other hand, finds no reciprocals in its serum, except to other members of the genus Artemisia, so its identification is definitely to the genus. Further than this we cannot go for it has already been shown that the different species of Artemisia are antigenically identical (Wodehouse, 1948).

These experiments establish the fact that if sites are sensitized with two sera possessing inversely dominant sensitizations, tested and desensitized with an unknown extract, then each tested with the allergen of its predominating sensitization, one positive and one negative reaction indicate that the unknown extract contains only the allergen that failed to give a reaction; both tests negative indicate both allergens present; and both tests positive indicate neither present. This may be expressed graphically as:

$$a \rightarrow X \rightarrow A \begin{cases} \nearrow + = \text{A absent from X} \\ \searrow o = \text{A present in X} \end{cases}$$

$$b \rightarrow X \rightarrow B \begin{cases} \nearrow + = \text{B absent from X} \\ \searrow o = \text{B present in X} \end{cases}$$

if a and b represent reagins, A and B their homologous allergens, and X the unknown solution.

(References on Page 814)

PERSISTENT COUGH AND BRONCHOSPASM DUE TO EXPOSURE TO FUMES FROM RANGE OIL

A New Clinical Syndrome

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ABOUT nine years ago, while staying at a summer camp, I developed a short, hacking cough, which lasted three days and then ceased, only to recur in the same way on the following weekend. Suspecting that it might be the oil range, exposure to which in the past on several occasions had given me a laryngeal "catch," I gave it no further thought until several months later when a patient presented himself with a clinical history similar to mine. With elimination of the oil range, he had a complete permanent remission.

During the following winter, a three-year-old boy was referred to me for studies. He had suffered from a continuous hacking cough, worse in the winter and more marked at night, and associated after the second year with wheezing. He came from northern Maine and had been in Boston for three days when his symptoms ceased. The cough was so similar to mine that a diagnosis of nonpassive expiration asthma due to range oil fumes was made. Subsequent experimental change of environment proved that exposure to range oil fumes almost always caused coughing and wheezing. Absence of exposure to the fumes of range oil was associated with complete freedom from symptoms.

Gradually, with further experience as the clinical picture became more clearly defined, more patients presenting the full constellation and its associated syndromes were recognized, and in all, some forty-one case-histories have been gathered together in the subsequent nine years.

In the average patient, the onset is so insidious that he cannot ascribe an exact date to his initial symptoms. The cough usually comes on in the fall as early as the first cool days, and in New England, while ragweed pollen is still prevalent. The cough grows worse with the onset of winter, reaching its utmost in severity by March or April. In some patients it may decrease or become completely quiescent during the summer months, depending, of course, upon the pattern of life followed in the patient's home.

For the younger children, who are not as yet in school, the symptoms may be continuous. Those at school may have periods of freedom during the week, with exacerbations during the weekend, being much worse when bad weather keeps them indoors and improved when in the outside air. For older people, the ones at home, usually the housewife, is worse off than her husband or sons unless their occupations keep them at home, as it does among coastal fishermen and farmers, who in the sections further north have minimum outdoor winter activities. Not all members of the

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family are equally affected, the very young and the very old being the chief sufferers.

In patients who have suffered a long-standing cough of this type there may be an associated sinusitis, a bronchitis, a history of frequent upper or lower respiratory tract infections, progressing to a chronic bronchitis. Young and old present an emphysema, the former due to the constant forceful expiration, which in the latter is also associated with changes due to age. In the absence of infection there is little or no phlegm, the cough being low in the throat and therefore often completely nonproductive. It is recalcitrant to any and all drug treatment, except for massive doses of narcotics which, of course, are acting, in all the doses given, as general sedatives rather than cough depressants. In these patients expectorants have no expectorant action, and the cough, chronic, persistent, hacking and unproductive, keeps the patient awake and often makes life miserable for the members of his family and occasionally his neighbors who cannot possibly escape it and stay asleep. In some families several members may be affected, their symptoms differing only in degree. The elimination of the oil for the patient most seriously ill has resulted in decreased illness for all of his group. Occasionally, however, only one person shows this spastic response.

When wheezing develops, it is severe and the patient becomes a medical emergency. Removal to the hospital changes the environment, and so these patients, who do not directly respond to the medicines given them, nevertheless improve, going from dire illness to complete recovery in two or three days. To the despair of the patient, his family and the physician, the cough may recur within an hour or two after returning home or may be delayed for one or two days, presenting itself as a short double expiratory hack every few minutes, gradually growing more severe and continuously barking before developing into a wheeze. It may occasionally begin as a catch in the throat, and some patients have learned that they are sometimes relieved by keeping water boiling continuously on the very stove responsible for their symptoms. This may decrease the marked dryness, but does not markedly affect the basic irritation.

When the patient resides in such geographical areas in which oil stoves are in general use, he may experience no clinical change related in any way with change in environment. His symptoms are present at his friends, his relatives, the corner general store, the local garage, the post office, and the club. Sometimes, to add to his mystification, exposure will not result a cough. A mild winter may expose him to more fresh air and lessen his symptoms, while a severe winter may expose him to more of the irritant fumes which make him much worse. At his lowest point, the very nadir of his symptoms, when he is chronically fatigued and worn down by lack of sleep, infection, usually a pneumonia, may intervene, and if the patient is treated away from home, both conditions are successfully cured, the one, of course, to recur. Those patients who have suffered successive pneumonia

for several succeeding winters may go south or southwest and, by the elimination of the range oil fumes, rather than the geographical location, become completely well.

In some there is, naturally enough, a personal or family history of allergy. They follow dust precautions and take injections of house dust with no effect. Some are given vaccines, stock or autogenous, achieving questionable results. Careful study in some of the larger medical centers usually leads to a diagnosis of psychoneurosis. Some of these patients have had psychotherapy, with which no fault can be found since the organic cause being unknown, a functional reason, arrived at by exclusion, was postulated.

One of our male patients was diagnosed as suffering from "a depletion syndrome" and given a high caloric, high vitamin diet and testosterone, responding well while hospitalized but proving himself completely recidivist with a relapse on returning home.

One of the two case histories to be given is illuminating, in that the patient presented a concomitant pansinusitis, supposedly the cause of his wheezing but nevertheless still present and causing no symptoms following elimination of the exposure to range oil fumes.

The patient, fifty-five years of age, presented symptoms which began in August, 1944. Skin tests by four allergists at intervals since have been completely negative. A chest x-ray is said to have demonstrated a mass, for which a bronchoscopy was done. No diagnosis was made, and the mass has since disappeared. X-rays of the sinuses showed both antra to be dense. The patient was given emergency treatment for acute bronchial asthma in August, September, October and November of 1946, each attack clearing completely during a hospital period of three days. Some small polyps were removed in January, 1947. A diagnosis of pansinusitis was made, and the patient was hospitalized again for acute bronchial asthma in February, 1947. While in Florida for all of March he was symptom-free. Two days following his return in April he required hospitalization. The cough persisted daily with severe wheezing for one night in June, three in July and two in August and then with increased frequency, several times monthly with three hospital admissions for emergency treatment in September, followed by continuous wheezing for the winter months. Elimination of range oil on March 3 gave him an almost complete remission to date (June 1), except that one Luasmin capsule was taken on March 8 because he thought an attack (which, by the way, did not materialize) was imminent. He overate on March 23 and suffered from dyspnea lasting approximately thirty minutes, which however required no medicine. He gained 11 pounds in six weeks. He sleeps all night and on the occasion of his last visit reported that for the first time in five years he had been able to spend an afternoon splitting logs.

The second patient's history is classical in its simplicity. A girl of five was seen on April 28, 1948, because of a catch in her throat associated with a short, hacking cough and difficult breathing. Her symptoms were occasionally present during the day but were always worse at night, reaching a climax at about 3:00 a.m. Wheezing attacks occurred at intervals of several days and lasted three days for four attacks in October. There were occasional remissions up to one month. On the same day, and before she returned home from the physician's office, the stove, which was of a gas and oil type, was turned off, with complete remission, lasting now for exactly one year.

The laryngeal bronchospasm, when due to exposure to range oil fumes, is apparently caused by the end-products of the combustion of kerosene (range oil, coal oil) in the wick variety of burner of the type surrounded by three perforated cylinders and known to act on "the reverse flame principle." With this type of burner, the air is sucked by natural draft into the holes of the perforated shells which surround the space which is filled with oil vapor, due to the vaporization of the kerosene which lies at a constant level in a receptacle at the base of the wick, the yellow flames of which merely vaporize the oil. The true flames, which are blue, consist of air burning in an atmosphere of hydrocarbon gas, in accordance with what is known as the aldehydeous combustion process.

Any cause of incomplete combustion, as for instance when the cylindrical shells are too cold, when there is not sufficient air, or when the level of the oil is not exactly right, leads not to the formation of soot, which is a product of destruction, but to the occurrence of invisible acrid vapors containing aldehydes. These aldehydes are the typical intermediate products of this type of blue flame combustion. The asthma seen in warmer parts of the country where coal oil stoves are used only intermittently for occasional cold spells is probably due to these fumes.

The long-chain hydrocarbon molecules in kerosene burn gradually, like fuses, forming first high alcohols, then fatty acids and aldehydes or peroxides, which are themselves gradually transformed into lower alcohols, organic acids and aldehydes, at the same time splitting off formaldehyde molecules. These eventually burn separately either to carbon dioxide and water or to carbon monoxide and water, or are broken down thermally to carbon monoxide and hydrogen.

An imperfect burner of this type gives off acrid, invisible, tear-drawing vapors without the slightest trace of soot. These vapors invariably contain varying amounts of formaldehyde. Some patients are affected by a little, while others require larger doses before symptoms occur.

This process is quite different from that seen in a kerosene lamp, in which the center of the flame consists of pure hydrocarbon vapor exposed to strong radiation of heat from surrounding flame fronts, resulting in a decomposition of the oil gas in the center before it has an opportunity of combining with oxygen. The carbon particles thus formed are set glowing as they reach the flame front on its inner side and are burned as they gradually traverse the flame to its outer side. The kerosene lamp is an example of the carbonic type of illumination as compared to the aldehydeous combustion, and when imperfect, it deposits soot and does not form aldehydes, formaldehyde, or methane.

The fumes are not seen with fuel oil or with a pot-type of burner as used in some heaters using range oil. The venting of the stove may sometimes help, but since the wick is upright and directly beneath the stove venting is never complete. The older the stove the worse the fumes; but the older the house, frequently the better the patient, since the newer

houses have fewer structural defects providing unwanted ventilation. The wick, which may be asbestos or fibre, is apparently not important, excepting as the level of the oil may cause the deposition of soot or gums on part of the wick, resulting in incomplete combustion. The higher the quality of the oil, the less difficulty, but no oil is completely free of the causative materials, since they are due to the type of combustion rather than to the composition of the oil.

The kerosene or range oil as stored does not itself cause difficulty, although in some patients as fumes in clothing they bring on an attack. Some of the patients are also sensitive to other nonspecific irritants, as smoke from coal (soft or hard), wood fires, refrigerant gases, frying oils which are being heated at too high a temperature so that acrolein and other burned products are given off, and in some cases, to tobacco smoke, more from pipes and cigars than from cigarettes.

Since Metazene mist combines with unsaturated sulfur and nitrogen compounds and will completely neutralize formaldehyde, it will be interesting to note its effect on these patients as the present studies are extended.

Of the utmost importance is the fact, however, that these patients, when bronchospastic, are with very few exceptions (and these perhaps more coincidental than real) labeled as intrinsically asthmatic. Infection, however, when present is not causally related to their symptoms. The range oil fumes may, of course, act as a nonspecific irritant in those otherwise atopic.

Since any cough due to any cause may cause marked active expiratory effort and this in itself can lead to bronchospasm, a special descriptive term is warranted.

In actuality, the range oil fumes cause a chronic coughing, leading to bronschospasm. Since, medically speaking, our thinking is usually in reverse sequence, these patients must be labeled as having a wheeze due to continuous nonpassive expiration caused by a chronic cough following exposure to fumes from range oil.

A careful search of the literature has brought to light no previous description of this syndrome, the existence of which must have been suspected and known although not described. If it has been previously described, the reference would be welcomed by the author so that the full credit can be given.

75 Bay State Road

AEROSOLS

I. The Urinary Excretion of Inhaled Phenolsulfonphthalein Mists

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SINCE the initiation of penicillin aerosol for topical therapy of the lungs by the Chemical Corps (then the Chemical Warfare Service) in 1942, the way in which antibiotic aerosols are deposited in the respiratory tract has not been adequately scrutinized.[1,4] This communication is part of a series which will endeavor to place the use of aerosols on a more quantitative basis.[1] The experiments with phenolsulfonphthalein aerosols were begun by one of us (H. A. A.) in the spring of 1946, when the standard solution of phenolsulfonphthalein used in renal function tests was orally inhaled as an aerosol. This solution contained 6 mg. of the dye per c.c. Although traces of the dye appeared in the urine, it was evident that this concentration was too low to lend itself to quantitative experimentation. Further investigations with Reiter in 1947 placed the excretion of the dye after inhalation on a more practical basis for the study of lung absorption (permeability). Finally 2.5 c.c. of a sterile solution of the dye, containing approximately 50 mg. of the dye per c.c., was used in a De Vilbiss No. 40 nebulizer equipped with nasal tips. These tips fit so snugly in the nose that with inspiration, with the air or oxygen at 10 liters per minute, the aerosol acts as if it were in a closed system, goes directly to the lungs through the nose. None escapes into the atmosphere except that exhaled. However, only a part of the dye delivered by the nebulizer actually reaches the lungs themselves. Deposition occurs in the nose and the pharynx with a certain amount swallowed. Nevertheless, this technique apparently provided a simplified approach for the study of aerosols in man because a fairly consistent curve of renal excretion occurred in normal and allergic individuals. In our preliminary work, it was shown that within two hours, 4 to 10 mg. of the dye were excreted in the urine, with the total dye in the urine reaching a limiting value at approximately eight hours. In our first group of five normals approximately 8 to 10 mg. of the dye appeared in the urine within two hours. Later experiments, however, disclosed that this value was rather high and that ostensibly normal individuals could excrete much less. Several questions arose. Since deposition occurs in the nose, what was the effect of shrinkage on the nasal mucous membrane? What effect would the stabilization of the particle size by means of glycerol have on the deposition and absorption of the dye in the lungs?[1] How much of the dye on the nasal mucosa was absorbed into the blood stream

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TABLE I.

URINARY EXCRETION OF NEBULIZED PHENOLSULFONPHTHALEIN—VENT OPEN

Nasal route except in A-3 where oral route was used. Original volume in nebulizer—1 c.c., except in A-8 and A-9 where 1.5 c.c. was used.

Experiment	Original Dye in Nebulizer Mg.	Dye Delivered on Nebulization Mg.	Completion Time Min.	The dye excreted in mg. is given in hours: 1, 2, 3 and 4. The numbers in parenthesis refer to the number of c.c. of urine excreted for each period.			
				Hours:			
				1	2	3	4
A-1 (CR)	39.5	14.5	12	0.85 (632)	0.62 (463)	0.30 (165)	0.26 (93)
A-2 (BK)	39.5	4.9		0.41 (568)	0.12 (323)	0.02 (80)	
A-3 (BK)	66.0	29.0	15	1.44 (375)	1.80 (450)	1.09 (75)	0.74 (50)
A-4 (CR)	66.0	18.5	8	1.52 (198)	1.07 (516)	0.56 (215)	0.34 (75)
A-5 (JS)	66.0	17.5		1.64 (180)	1.59 (155)	0.79 (85)	0.60 (65)
A-6 (CR)	82.0	10.5	5	1.11 (415)	0.72 (440)	0.33 (74)	0.36 (77)
A-7 (BK)	82.0	7.0		1.03 (668)	0.51 (78)	0.13 (66)	
A-8 (CR)	146.0	36.0	10	6.11 (490)	3.58 (230)	2.12 (95)	1.17 (155)
A-9 (HA)	146.0	46.0	10	1.93 (101)	1.45 (110)	1.20 (65)	0.65 (40)

No irritation except in A-3. A-9 had cough, fever and prostration 3 hours after experiment.

and appeared in the urine? What fraction of dye delivered to the patient appeared in the urine? Not all of these questions have been fully answered. However, sufficient data have been accumulated to give in this communication a further report on the urinary excretion of the nebulized phenolsulfonphthalein under various conditions and to make more explicit certain problems connected with (1) aerosol therapy of the lungs in general and (2) the administration of toxic and antigenic aerosols with standardized nebulizers.

METHOD

In general, the method briefly described[2] was employed with certain differences. The standard procedure for renal function was followed except that the dye was inhaled. The bladder was emptied and the subject took 500 c.c. of water. Specimens were obtained hourly from the start of the inhalation. Since, in Tables III and IV, it was assumed that the volume velocity recorded on the flow meter at the beginning of the tube connected to the nebulizer was approximately equal to that at the end of the nebulizer, the value for the volume velocity may be slightly less than given. Nasal tips and L-tube of the De Vilbiss No. 640 combination were employed. The dye was determined by means of a Coleman spectrophotometer. Urinary pigments introduce an error of 0.2 to 0.3 mg. at low concentrations of

TABLE II. URINARY EXCRETION OF NEBULIZED PHENOLSULFONPHTHALEIN

Time of each experiment, 15 minutes. Vent was open. Nasal route was used. An initial volume of 2.5 c.c. was used, with 125 mg. of the dye.

Experiment	The dye excreted in mg. is given in hours: 1, 2, 3, and 4. The numbers in parenthesis refer to the number of c.c. of urine excreted for each period.			
	Hours:			
	1	2	3	4
B-1 (CR)	5.0 (200)	2.7 (165)	1.2 (55)	0.63 (45)
B-2 (CF)*	2.9 (315)	1.9 (100)	1.1 (70)	0.88 (70)
B-3 (JS)	6.1 (320)	3.7 (200)	2.3 (145)	1.5 (80)
B-4 (MT)	6.1 (120)	2.1 (90)	1.25 (70)	0.42 (55)
B-5 (CR)**	5.7 (75)	3.3 (45)	1.65 (165)	0.95 (40)
B-6 (BS)*	3.2 (40)	2.3 (40)	1.25 (40)	0.75 (35)

*These subjects are allergic and showed no reaction.
**Had slight irritation. Reaction of fever and cough.

dye. In the A and B series of experiments (Tables I and II) air pressure with a Gast pump was obtained. In the remaining experiments, oxygen was utilized. Some of the subjects preferred the oxygen to the air pump. Whether this preference was psychological or not has not been ascertained.

It is important to note that the dye was nebulized only when the finger was placed over the Y-tube so that the time of nebulization was markedly influenced by the inspiratory pattern of the subject. This will be taken up in detail in a subsequent communication.

It is believed on the basis of experiments now in progress that for every 10 mg. of dye swallowed, not more than 0.5 mg. of the dye will appear in the urine. In general, nasal deposition and swallowing will represent a small constant error in the experiments and under present circumstances cannot readily be avoided. Quantitative data with radioactive solutions might yield better data, but they are technically so difficult that it appears more pertinent to our present therapeutic procedures with antibiotics and sympathomimetic amines to study the behavior of a simple substance like phenolsulfonphthalein where deposition of the dye is readily observed in the nose and pharynx and its excretion can be easily followed in the urine. The presence of dye in coughed-up pus is always observed and studied, as previously reported.[2]

TOXICITY

Reactions (cough, fever and weakness similar to a virus infection) have been observed on five occasions after inhaling the dye. It is not known whether these reactions are due to (1) irritation by the dye, (2) activation of a virus, (3) sensitization to the dye or (4) accidental occurrence of

respiratory infection. In any event, about 100 inhalation tests have been made in which no reaction to the dye was observed. Thus, one of us (B.S.) has inhaled the dye more than ten times with no irritation or reaction whatsoever.

Our animal toxicity experiments may be briefly summarized: Three white mice, approximately 50 gm. each and nine months old, were exposed to phenolsulfonphthalein aerosols, in which the dye was nebulized for seven hours over a period of three days. There were no objective differences from the controls receiving saline aerosols. Three gray mice, each weighing 30 gm., three months old, were given 1 c.c. of the dye intraperitoneally, each c.c. containing 18 mg. Within ten minutes, the nose, tail, ears and the skin became red. The injected dye was readily observed in the blood vessels of the ears. There was no obvious effect on activity as compared to the controls. The skin coloring disappeared within six hours. Red colored urine was observed in the cage. Higher concentrations were then given intraperitoneally with 2 c.c. of the dye containing 18 mg. per c.c. to three gray mice. The same three gray mice were used as in the previous experiments. In 3.5 minutes the body became red and the animals became listless in twenty minutes. This effect wore off in seven hours when the mice became indistinguishable from animals which had no intraperitoneal injection. A fourth experiment was done in which six gray mice received phenolsulfonphthalein aerosol in a dessicator for six continuous hours. The animals were killed and at autopsy nothing abnormal was found. Sections were made of the animals killed immediately, three hours and seventeen hours after exposure. There were no microscopic changes observed. Animals which had received phenolsulfonphthalein intraperitoneally and the saline controls were killed fourteen hours later. In both sets of animals there was evidence of peritonitis. In the animals given the dye, application of alkali to the lungs, kidney and liver showed that the dye still persisted.

EXPERIMENTAL RESULTS

Table I contains experiments designated as Series A. These were undertaken to determine the approximate effect of initial concentration of the dye in the nebulizer on the urinary excretion of dye, in order to ascertain the minimum concentration which would give reproducible and significant concentrations in the urine. In addition, they represent one type of procedure recommended currently for aerosol therapy. Experiments A-1 through A-7 utilized 1 c.c. of the liquid as the initial volume in the nebulizer with a dye content as noted in the table. Inhalation was continued by the subject until the nebulizer failed to operate because of insufficient volume of liquid. These data are of significance because they indicate the possibilities of irregularity in the delivery and absorption when a similar procedure is followed with antibiotic therapy. After experiments A-1 to A-7 were completed, it was believed that the dye excretion in the urine was

TABLE III. URINARY EXCRETION OF NEBULIZED PHENOLSULFONPHTHALEIN
Time, 15 minutes. Vent closed. Nasal route used in each case.

Experiment	PSP Solution Nebulized	Diagnosis	Mg. Delivered to Patient and Per Cent Delivery	The dye excreted in mg. is given in hours. The numbers in parenthesis refer to the volume of urine excreted for each period.			
				1	2	3	4
C-1 (CF)**	100,000 u. penicillin G with 67 mg. PSP in 2.5 cc.	Bleeding duodenal ulcer and lues.	30 mg. 55% del.	1.7 (450)	1.8 (150) 2½ hrs.	1.0 (90) 3½ hrs.	0.5 (60) 4½ hrs.
C-2 (WC)	100,000 u. penicillin G with 67 mg. PSP in 2.5 cc..	Diabetic acidosis	21 mg. 70% del.	1.0 (180)	0.8 (125)		
C-3 (LV)	100,000 u. penicillin G with 100 mg. PSP in 2.5 c.c.	Post AP and schistosomiasis.	42 mg. 58% del.	2.0 (100)	1.4 (45)	1.3 (38)	
C-4 (CF)**	1,000,000 u. penicillin G with 66 mgms in 1.2 c.c. H_2O and 1 c.c. saline.		22% del.	0.8 (145)		1.1 (180) 3½ hrs.	
				Serum penicillin levels 0.26 u. at 1 hr.—0.1 u. at 2¾ hours.			

**Same patient.

probably too low. The volume of the dye in the nebulizer was increased to 1.5 c.c., the total dye in the nebulizer being 146 mg. and the experimental time ten minutes. At this time it was noted that with this technique the depth of inhalation might markedly influence the absorption and excretion of the dye, although this could not be ascertained. There are wide differences between experiments A-8 and A-9. In experiment A-8, almost 10 mg. of the dye was excreted in two hours, with only 36 mg. being delivered to the subject. In experiment A-9, less than 4 mg. was excreted even though the subject retained 46 mg. of the dye. The reaction of H. A. A. to the dye in experiment A-9 with cough and fever was subsequently shown by C. R. in a later experiment. The reactions to the dye will be discussed in detail in a future communication. Table II is the second series of experiments performed with the dye in a further attempt to standardize the study of lung absorption and permeability with phenolsulphonphthalein. The preliminary screening experiments in Series A showed that adequate urine excretion was accomplished by inhaling the aerosol produced by a 10 per cent solution for ten minutes. Despite the negative results of the toxicity experiments in animals, it was still believed that the dye might be irritating to the pulmonary mucosa. A reduction of dye concentration to 5 per cent with an increase of the experimental time to fifteen minutes was decided upon to offset the disadvantages of the higher concentration of the dye. In these experiments, the nebulizer vent was open. As in the experiments with injected dye and the nebulized dye in Series A, readily detectable quantities of the dye appeared in the urine ten to fifteen minutes after the start of the inhalation of the aerosol. The data in Table II show that considerable quantities of the dye appear in the urine after two hours. However, there

are wide differences in the quantity of dye appearing in these normal subjects. On the basis of these data, there is a certain element of regularity in the appearance of the dye. Thus subject C. R. showed at the end of two hours 7.7 and 9 mg. of the dye. There is an important difference, however, between C. F. and J. S. which cannot be accounted for by any obvious differences of the two subjects or by the presence of pathology. Because of the occurrence of two reactions, experiments were continued as in Series C, illustrated in Table III, in which penicillin was administered together with the dye. The experiments were conducted, as in Series B, with the exception of C-4. The experiments in Table III illustrate that the presence of penicillin in dye-penicillin mixtures apparently does not interfere with the absorption of the dye in the lung. It is of interest that these experiments were conducted under conditions resulting in 22 per cent to 70 per cent nebulization of dye (the nebulizer residue was rediluted) even though the total experimental time was always fifteen minutes. Evidently we are dealing with variables which are not necessarily in the equipment but inherent in the method of doing the test. It became of importance to ascertain how reproducible the test was and how other factors influence the results. The electric charge and size of penicillin and the dye are somewhat similar. It should therefore be noted that the delivery of the dye also may indicate the delivery of penicillin and other drugs under the experimental conditions. In other words, subject D. F. probably would have retained 55 per cent of 100,000 units following our procedure. In experiments on the same subject, C-1, and later C-4 where the nebulizer was washed out, because of difficulties in respiration only 22 per cent delivery was obtained. However, fairly high values of penicillin units were obtained in the blood. This shows the advantage of using high concentrations of penicillin in the nebulizer as advocated previously.[1,2]

In Table IV are data which explain certain of the variables mentioned in the introduction. In Column 1 are the initials of the patients and the date; Column 2 is the diagnosis; Column 3 shows the presence or absence of 20 per cent glycerin; Column 4 indicates the presence or absence of Privine to shrink the mucous membrane of the nose. Column 5 is the time in minutes of the experiment; Column 6 gives the volume velocity in liters per minute, and Column 7, the volume of urine. Column 8 lists the mg. of dye in the urine; Column 9 shows the residue in the nebulizer; Column 10, the per cent of dye delivered to the patient; Column 11, the dye in the urine after two hours. In view of the large number of variables present in experiments of this type, it was of interest that in patient A. W. there was good agreement in the volume of dye excreted after two hours. In the first experiment 1.38 mg. of dye was excreted, and in the second an identical amount. This agreement, of course, is accidental. The per cent delivery of the dye is of interest since of 100 mg. of the dye in each experiment, 12.5 mg. of dye was delivered to the patient. Of this 12.5 mg., 10 per cent appeared in the urine in two hours. Since the concentration in

TABLE IV. URINARY EXCRETION OF NEBULIZED PHENOLSULFONPHTHALEIN

The vent was closed. When Privine was used, a 0.1 per cent solution was employed. Two similarly calibrated De Vilbiss No. 40 nebulizers were used. Two c.c. of 5 per cent PSP was used as the initial volume and concentration.

Experiment and Date	Diagnosis	Glycerine 20%	Privine	Time in Min.	Volume Velocity l/m.	Volume of Urine Excreted c.c.		Mg. PSP Excreted		Residue in Nebulizer Mg.	Per Cent Del.	Total in Two Hours Mg.
						Hour		Hour				
						1st	2nd	1st	2nd			
A. W.	Asthma											
(a) 4/7		No	Yes	15	7	30	30	0.63	0.75	—	—	1.38
(b) 4/27		Yes	No	15	7	0	50	0.00	1.38	87.5	12.5	1.38
E. W.	Hay fever											
(a) 4/8		No	Yes	15	8	360	325	0.63	0.85	—	—	1.48
(b) 4/15		No	No	15	7	140	320	0.50	0.27	85.0	15.0	0.77
(c) 4/22		Yes	No	15	7	280	230	0.56	0.68	92.5	7.5	1.24
(d) 4/28		Yes	No	15	7	390	160	0.75	0.65	95.0	5.0	1.40
T. A.	Gangrene of right toe	2.5% PSP										
(a) 4/13		No (by Mo.)		10	5	410	300	0.00	0.002	41.6	19.0	0.002
(b) 4/19		Yes	No	15	7	475	105	0.75	0.22	89.0	11.0	0.97
(c) 4/21		Yes	No	15	7	450	240	1.05	0.67	89.6	10.4	1.72
J. I.	Bronchiectises											
(a) 4/14		No	Yes	15	7	310	160	3.38	3.00	86.1	13.9	6.38
(b) 4/21		Yes	Yes	15	7	240	90	2.34	2.45	90.0	10.0	4.79
(c) 4/28		Yes	Yes	15	7	230	80	2.05	2.04	83.0	17.0	4.09
M. K.	Hay fever											
(a) 4/15		No	Yes	12	7	530	320	1.75	2.3	78.0	22.0	4.05
(b) 4/22		Yes	No	15	7	570	330	1.15	1.6	89.8	11.0	2.75
(c) 4/29		Yes	Yes	15	8	410	220	1.50	1.23	85.0	15.0	2.73
D. F.	Infectious mononucleosis											
(a) 4/27		Yes	No	10	7	—	190	—	0.58	—	—	0.58
(b) 5/3		No	No	15	8	70	35	0.33	0.24	87.5	12.5	0.57
F. P.	Prepyloric lesion											
(a) 5/25		No	No	15	7½	200	75	1.4	2.1	72.0	28.0	3.5
(b) 5/27		No	No	15	9	200	210	2.15	3.0	75.0	25.0	5.15
(c) 6/3		No	No	15	8½	315	120	1.95	2.15	77.5	22.5	4.10
(d) 6/9		No	No	15	8½	235	210	1.71	2.43	75.5	24.5	4.14

the urine after an intravenous administration of 6 mg. of the dye would be about 70 per cent of the dye administered, it would appear that approximately between 10 per cent and 20 per cent of the dye delivered to the patient in this way, appeared in the urine in two hours. In patient E. W., four experiments, (a) (b) (c) and (d), were done in which these variables were studied in more detail. It was found, however, that there was considerable variation in the amount of dye delivered to the patient. In addition, of some interest is the fact that in E. W.'s experiment (b) less than 0.8 mg. of the dye was delivered in two hours even though more of the dye was delivered to the patient by nebulization. This experiment emphasizes the fact that there were still variables which had to be considered. In patient T. A., 2.5 per cent solution of the dye was delivered by mouth because the 5 per cent solution was irritating. This experiment is excellent from the point of view of studying the effect of swallowing the dye. Prac-

tically no dye was excreted. At the end of two hours there were in experiment T. A. (b) 0.97 mg. of dye in the urine and in (c) 1.72 mg. of dye. After four hours, the same discrepancy appeared even though the delivery by the nebulizer was fairly constant. Patient J. I. had extensive bronchiectasis which did not respond to various types of penicillin therapy. He took the dye well except for the fourth time, when a reaction occurred. In two hours his excretion varied from 4 to 6.8 mg. Although this patient was experienced in breathing aerosols, it was nevertheless surprising to find the high excretion of the dye in the presence of extensive lung pathology. Similar experiments with patients M. K. and D. F. again showed the fluctuations. The data in Column 9, where a fairly wide difference in delivery of the dye under constant experimental conditions may be observed, offer a clue to the possible cause of the variation. The delivery of dye varies from 5 per cent to 20 per cent even though the total time of the experiment and the volume velocity of delivery of the gas is fairly constant. The experiments on patient J. I., and on the experienced normals in Tables I and II, as well as on patients with deep inspirations, were observed to be followed with higher excretions of dye. This led to the point of view that the variations were not so much due to baffling by the nose or the stability of the aerosol but to the conditions of experiment, in all likelihood connected with the character of inspiration or the inspiration time.

It is well known that the longer an aerosol is retained in the lung the greater the probability that the particles will be deposited; in other words, the greater the probability of collision of particles with the mucous membranes of the respiratory tract, the greater the probability of deposition. For this reason, it was decided to continue these studies in which not the total time of administration of dye was of importance but the *inspiration time*. An inspiration-time meter was devised which is described in a following paper of this series. This device measures the actual time in which the aerosol is inspired, the number of inspirations, and by means of auxiliary devices gives the character of the respiratory cycle as well as the total time. Since the volume velocity of the gas, the amount of dye delivered, and the conditions of delivery are known, a balance sheet may be obtained, in which more explicit data of the conditions under which the deposition of the dye in the respiratory tract occurs may be visualized.

DISCUSSION

These experiments have been reported in full because the present tendency in the use of the therapeutic aerosols is to give the patient the antibiotic or epinephrine, or whatever drug is indicated, in a nebulizer with brief directions and to hope for the best. This casualness in therapy should be replaced by a more quantitative procedure. It has been pointed out in previous communications that it is important to have the delivery of the nebulizers determined. It would be desirable to have the manufacturers of nebulizers certify that a given nebulizer is capable of delivering a given

quantity under specified conditions. Although it is not practical at this time to certify nebulizers in the way that thermometers are certified, in view of the fact that antibiotic, especially penicillin, aerosol therapy of the respiratory tract has become a standard procedure in the treatment of lung infections,[4] it appears that the errors inherent in the accidental variations of aerosol therapy are more than anticipated. Certainly, the data presented in Tables I to IV show that under ostensibly controlled conditions, with standardized nebulizers, with a substance as easily determined as phenolsulfonphthalein, there is probably great variation in the deposition in the lungs. Only by a study of the data, as indicated in the body of the paper, may the reader visualize how important the standardization of aerosol therapy is for the successful completion of topical therapy by means of aerosols.

SUMMARY

By means of phenolsulfonphthalein aerosols data have been obtained on the absorption of phenolsulfonphthalein from the lungs following inhalation of aerosols of this dye. The experiments were mainly carried out using the nasal route so that inhalation occurred in a closed system. The effect of baffling by the nose and upper respiratory tract as well as swallowing of the dye is shown to be of minor importance with the main quantity of the dye appearing in the urine dependent upon absorption through the mucous membrane of the lungs.

The study of the toxicity of phenolsulfonphthalein aerosols in mice showed that large quantities of this dye can be safely injected and inhaled without serious toxic effects. Five reactions in man have been observed during a course of about 100 tests of aerosol inhalation with fairly concentrated solutions and quantities of the dye. These reactions have been fever, cough and general weakness similar to a virus infection endemic in the vicinity where the experiments were done. Whether these reactions are due to irritation by the dye, activation of a virus, sensitization to the dye or accidental occurance of respiratory infection has not been ascertained. Otherwise there was no irritation produced by the dye administered in the way described.

The following variables have been studied and data presented pertinent thereto: (1) Effect of the initial concentration of the dye in the nebulizer on urinary excretion of the dye, (2) The effect of increasing the volume of the dye, (3) The effect of shrinkage of the nasal mucosa, (4) Absorption from the nasal mucosa and excretion in the urine, (5) the effect of glycerine to increase deposition and absorption of the dye in the lungs, (6) The reproducibility of renal excretion of the dye, (7) The ratio of the dye excreted in the urine to the dye delivered by the nebulizer to the patient. It is concluded from the experiments that a larger number of

(Continued on Page 806)

COMPARATIVE TOXICITY AND SIDE EFFECTS OF THE ANTIHISTAMINIC DRUGS

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THE ANTIHISTAMINIC drugs now in general use relieve symptoms in many forms of allergy—especially hay fever, vasomotor rhinitis and urticaria—but they also produce undesirable results, or side effects. Because of wide differences in the frequency and in the severity of the toxic reactions reported in human subjects, it is important to record the comparative toxicity and side effects of the various antihistaminic drugs.

The following drugs were compared at essentially equal therapeutic dose levels: Benadryl, Pyribenzamine, Neo-Antergan, Antistine, Histadyl and Neohetramine. These drugs were chosen because they are the most widely used. All contain the dimethylaminoethyl radical, with differences in the remainder of the molecule. The chemical structures are shown in Figure 1.

CLINICAL STUDY

Side effects were recorded only in patients receiving therapeutically effective doses. Many of the patients reported in this study have been taking several different antihistaminic drugs interchangeably from one to four years without disturbance in blood count, blood chemistry or urine. The present study is a comparison of the toxic effects produced with the use of Benadryl in 217 cases, Pyribenzamine in 126 cases, Neo-Antergan in 127 cases, Antistine in 97 cases, Histadyl in 89 cases, and Neohetramine in 111 cases.

TABLE I. RESULTS OF TREATMENT WITH BENADRYL

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	11	7	4	63.6
Vasomotor rhinitis	44	19	25	43.2
Bronchial asthma	80	24	56	30.0
Chronic urticaria	21	11	10	52.4
Acute urticaria	32	26	6	81.3
Miscellaneous allergies	29	12	17	41.4
Totals	217	99	118	45.6

Benadryl.—Two hundred and seventeen patients received Benadryl for symptomatic relief in seasonal and nonseasonal hay fever, acute and chronic urticaria, atopic and contact eczema, bronchial asthma, and miscellaneous allergies, as pruritus, allergic pharyngitis, gastrointestinal allergy, allergic conjunctivitis, migraine, vernal catarrh, and drug allergy. Doses of 50 mg. were administered whenever necessary for intermittent symptoms, and 50 mg. four times daily for continuous symptoms. Dosage had to be adjusted in many patients according to individual requirements. The dosage schedule employed was considered adequate because it was thera-

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peutically effective. Results of treatment with Benadryl are recorded in Table I, and the side effects in Table II.

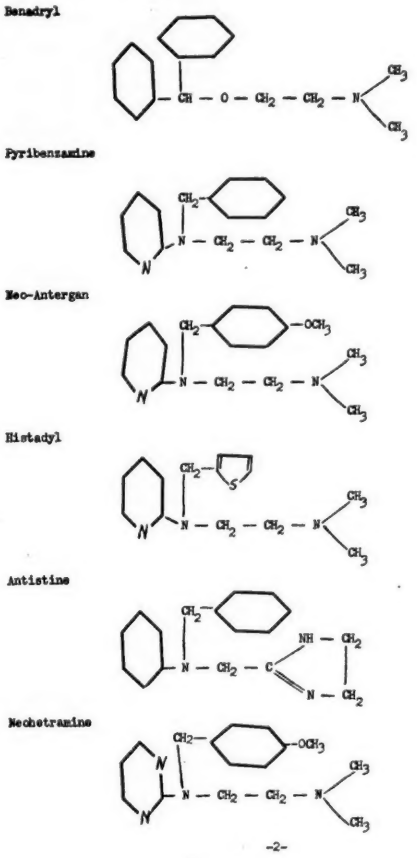

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Fig. 1.

Of 217 patients treated with Benadryl, 133 (61.3 per cent) complained of side reactions. In fourteen cases side effects were so severe that the drug had to be discontinued. Drowsiness, the most common, occurred in ninety-three (42.9 per cent) but gradually diminished in most patients and in some cases entirely disappeared with continuance of the drug. Dryness of the mouth occurred in forty-four patients; tingling, weakness or heavy sensation of the hands in thirty-two; headache in twenty-one; dizziness in fifteen; nervousness in eight; vomiting in four; weakness in two, and diarrhea in one. Patients complained of one to four different side effects, but most reported that the untoward reactions either diminished or disappeared as treatment continued. In several cases there were unusual

reactions: mental in-co-ordination in three; narcolepsy in two; and one patient slept for twenty-four hours after one 50 mg. dose of Benadryl. One felt as though he were "walking on air." Another, after 50 mg. of

TABLE II. BENADRYL—SIDE REACTIONS

Total Cases—217; Reactions—133 (61.3%)

Side Reaction	*Occurrence*
Drowsiness	93
Dryness of mouth	44
Tingling, heaviness or weakness of hands	32
Headache	21
Dizziness	15
Nervousness	8
Tinnitus	8
Vomiting	4
Mental in-co-ordination	3
Narcolepsy	2
Weakness	2
Diarrhea	1

Benadryl, was almost struck by an automobile twice in an hour, and became so emotionally disturbed that she refused to leave the hospital for twenty-four hours. In one case the patient became so drowsy driving his car that he had to park on the side of the road and sleep for two hours.

Pyribenzamine.—This group consisted of 163 cases, as follows: hay fever, 112 cases; vasomotor rhinitis, eighteen cases; bronchial asthma, nine cases; chronic urticaria, six cases; acute urticaria, one case; allergic eczema, twelve cases; and contact dermatitis, five cases. The dosage used was 50 mg. whenever necessary for intermittent symptoms, and 50 mg. every four hours for continuous symptoms. Results of treatment with Pyribenzamine are recorded in Table III.

TABLE III. RESULTS OF TREATMENT WITH PYRIBENZAMINE

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	112	82	30	73.2
Vasomotor rhinitis	18	10	8	55.6
Bronchial asthma	9	1	8	11.1
Chronic urticaria	6	5	1	83.3
Acute urticaria	1	1	0	100.0
Allergic eczema	12	5	7	41.7
Contact dermatitis	5	3	2	60.0
Totals	163	107	56	65.6

Side effects were recorded for 126 of the 163 patients treated with Pyribenzamine. Of these 126 patients, forty-five (35.7 per cent) complained of side effects, as tabulated in Table IV.

Side effects were fewer and not as marked as with Benadryl, but again unusual reactions were observed in several patients. One, an hour after taking 50 mg. of Pyribenzamine, became comatose for six hours; another was markedly drowsy and showed mental in-co-ordination while driving an automobile. He swerved from one side of the road to the other, several times narrowly avoiding accident. Another patient developed a tachycardia of 140 which lasted about twelve hours.

The usual side effects either diminished or disappeared, although Pyribenzamine was continued on the same dosage schedule. In a group of twenty-one patients taking 50 mg. of Pyribenzamine one to three times

TABLE IV. PYRIBENZAMINE—SIDE REACTIONS

Total Cases—126; Reactions—45 (35.7%)

Side Reaction	*Occurrence*
Drowsiness	17
Dizziness	8
Headache	8
Nausea	4
Nervousness	4
Weakness	3
Dryness of mouth	3
Fatigue	2
Tinnitus	2
Comatose	1
Mental in-co-ordination	1
Vomiting	1
Tachycardia	1
Irritability	1

each day for two years, monthly blood counts, blood chemistry and urine examinations remained normal.

Neo-Antergan.—This group consisted of 141 allergic patients who received 50 mg. of Neo-Antergan two to four times a day, depending on the duration of symptoms. The results of treatment are shown in Table V.

TABLE V. RESULTS OF TREATMENT WITH NEO-ANTERGAN

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	96	67	29	69.8
Vasomotor rhinitis	22	13	9	59.1
Bronchial asthma	15	2	13	13.3
Acute urticaria	1	1	0	100.0
Chronic urticaria	2	1	1	50.0
Allergic eczema	1	0	1	0.0
Pruritus	1	1	0	100.0
Angioneurotic edema	1	1	0	100.0
Vernal catarrh	1	0	1	0.0
Contact dermatitis	1	1	0	100.0
Totals	141	87	54	61.7

Of 141 patients receiving Neo-Antergan, thirty-five (24.8 per cent) experienced side effects (Table VI), most of which were mild and disappeared as the treatment was continued without change of the dosage schedule. Diarrhea (in eleven cases) was more frequent than with Benadryl, Pyribenzamine or Antistine. In this group there were no unusual or severe side effects.

TABLE VI. NEO-ANTERGAN—SIDE REACTIONS

Total Cases—141; Reactions—35 (24.8%)

Side Reaction	*Occurrence*
Drowsiness	13
Nausea	11
Diarrhea	11
Abdominal cramps	8
Headache	4
Dizziness	3
Tachycardia	4
Weakness	2
Sweating	2
Pruritus	2
Fatigue	1
Dryness of mouth	1
Vomiting	1
Nervousness	1

Antistine.—Antistine was administered to 111 patients. Ninety-seven of this group received 100 mg. (the therapeutically effective dose) every four hours whenever necessary to control symptoms, and side reactions were carefully recorded. Twenty-two (22.7 per cent) reported side effects. Table VII summarizes the results of treatment with Antistine and Table VIII the side reactions.

TABLE VII. RESULTS OF TREATMENT WITH ANTISTINE

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	80	45	35	56.2
Vasomotor rhinitis	17	9	8	52.9
Bronchial asthma	6	0	6	0.0
Chronic urticaria	5	4	1	80.0
Acute urticaria	1	1	0	100.0
Allergic eczema	2	1	1	50.0
Totals	111	60	51	54.1

TABLE VIII. ANTISTINE—SIDE REATIONS

Total Cases—97; Reactions—22 (22.7%)

Side Reaction	*Occurrence*
Drowsiness	6
Nausea	6
Headache	3
Dizziness	2
Tachycardia	2
Gastritis	2
Diarrhea	1
Fatigue	1
Nervousness	1
Sores in mouth	1
Insomnia	1
Abdominal cramps	1
Pruritus	1
Pharyngitis	1
Vomiting	1
Constriction of chest	1

In this series the usual side effects were encountered, as with Benadryl and Pyribenzamine, but were fewer and less severe. One patient complained of an unusual side effect—constriction of the chest lasting two hours. Because of the possibility of coronary artery disease, she was referred to the hospital. However, her blood pressure remained normal, sedimentation rate was 12 mm. per hour, and the electrocardiographic tracing showed no evidence of coronary disease or myocardial damage. Two weeks later, administration of 100 mg. Antistine by mouth again produced constriction of the chest.

Histadyl.—Histadyl was administered to eighty-nine allergic patients in doses of 50 mg. one to three times daily. In patients not relieved, but with no severe toxic reactions, the dose was increased to 100 mg. Therapeutic results and side effects are shown in Tables IX and X.

TABLE IX. RESULTS OF TREATMENT WITH HISTADYL

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever	47	36	11	76.6
Vasomotor rhinitis	17	9	8	53.9
Bronchial asthma	13	2	11	15.4
Acute urticaria	5	4	1	80.0
Chronic urticaria	3	2	1	66.6
Allergic eczema	2	1	1	50.0
Contact dermatitis	2	1	1	50.0
Totals	89	55	34	61.8

Of eighty-nine cases, eighteen (20 per cent) developed side effects but no unusual reactions were encountered in this group. Drowsiness and gastrointestinal symptoms were the most common side effects, but drowsiness was not severe enough to warrant discontinuance of the drug.

TABLE X. HISTADYL—SIDE REACTIONS

Total Cases—89; Reactions—18 (20%)

Side Reaction	*Occurrence*
Drowsiness	9
Dizziness	2
Dryness of mouth	2
Nausea	3
Abdominal cramps	2
Weakness	1
Tachycardia	1
Fatigue	1
Nervousness	2

Neohetramine.—One hundred eleven patients received Neohetramine, generally in doses of 50 mg. one to four times a day. In some cases 100 mg. three to four times daily was necessary to relieve the symptoms. In this group also the amount and frequency of the dose had to be adjusted, for many of the patients, to suit individual requirements. The results of treatment with Neohetramine are recorded in Table XI.

TABLE XI. RESULTS OF TREATMENT WITH NEOHETRAMINE

Allergic Condition	*Number of Cases*	*Relief*	*No Relief*	*Percentage Relieved*
Hay fever (ragweed)	41	29	12	70.7
Hay fever (timothy)	7	5	2	71.4
Hay fever (trees)	5	4	1	80.0
Bronchial asthma	24	10	14	41.7
Vasomotor rhinitis	22	14	8	63.5
Allergic eczema	6	1	5	16.7
Chronic urticaria	5	3	2	60.0
Pruritus	1	1	0	100.0
Totals	111	67	44	60.4

Of the 111 patients treated with Neohetramine, eight (7.2 per cent) noticed side effects, but no unusual or severe reactions (Table XII). Two patients discontinued use of the drug, one on account of nausea and the other because of an exacerbation of asthmatic symptoms. Seven of eight patients experienced one side reaction, and one patient, two. Mild drowsiness occurred in two and disappeared on further use of the drug.

TABLE XII. NEOHETRAMINE—SIDE REACTIONS

Total Cases—111; Reactions 8 (7.2%)

Side Reaction	*Occurrence*
Drowsiness	2
Dryness of mouth	1
Bitter taste	1
Nausea	1
Fatigue	1
Headache	1
Restlessness	1
Marked nervousness	1
Aggravation of asthmatic attack	1

DISCUSSION

Antihistaminic drugs have an important place in the symptomatic treatment of allergic diseases. Valuable adjuncts to the management of aller-

gies, they are not, however, a substitute for careful determination of specific etiologic factors, elimination of offending allergens where possible, or hyposensitization when necessary. Untoward reactions, not encountered in animal studies,[3,6,8,9] have occurred in human beings, and reports of serious and unusual side effects are beginning to appear in the clinical literature.[1,2,4,5,7,10-16] B. A. Sachs[11] has classified the toxic reactions encountered with Benadryl as neuropsychiatric, alimentary, cardiovascular, respiratory, genito-urinary, muscular and ocular, and it seems that the same classification can be applied to many of the other antihistaminic drugs. Severe untoward reactions are more common with higher doses.

The present study deals only with the side effects observed at therapeutically effective doses. Indeed, the dose schedule was adjusted to give essentially equal therapeutic results with all drugs studied. In general, the side effects, regardless of severity, disappeared within one to twenty-four hours after discontinuing the drugs.

Side effects occurred most frequently with Benadryl, with drowsiness of most common occurrence—in 93 of 217 cases (42.9 per cent). Dryness of the mouth was observed in forty-four of the 217 cases (20.3 per cent). Tingling, heavy sensation or weakness of the hands was reported by thirty-two (14.8 per cent); headache in twenty-one (9.7 per cent); dizziness in fifteen (6.9 per cent); nervousness in eight (3.7 per cent); tinnitus in eight (3.7 per cent). Other less frequent reactions were vomiting and diarrhea. Common side reactions varied from one to as many as four in some patients and were most frequent in the group receiving Benadryl. Benadryl also produced several unusual and severe side effects.

With Pyribenzamine drowsiness occurred in seventeen of 126 cases (13.5 per cent) and was not as marked as with Benadryl. Dizziness occurred in eight (6.3 per cent); headache in eight (6.3 per cent); nausea in four (3.2 per cent); nervousness in four (3.2 per cent); weakness in three (2.4 per cent); and dryness of mouth in three (2.4 per cent). Only occasionally did patients complain of fatigue, tinnitus, vomiting, palpitation or irritability. The common side effects also varied from one to as many as four in some patients.

With Neo-Antergan drowsiness occurred in thirteen cases (9.2 per cent); nausea in eleven (7.8 per cent); diarrhea in eleven (7.8 per cent); and abdominal cramps in eight (5.7 per cent). Those are the most common side effects. Other reactions are noted in Table VI.

With Antistine drowsiness was encountered in six cases (6.2 per cent); nausea in six (6.2 per cent); and many of the common side effects such as headache, dizziness and many others occurred occasionally. As a rule, the side effects encountered with Antistine were less severe than those following Benadryl or Pyribenzamine.

With Histadyl drowsiness occurred in nine cases (10.1 per cent); nausea in three (3.4 per cent); dizziness in two (2.2 per cent); dryness of mouth in two (2.2 per cent); and abdominal cramps in two (2.2 per cent). Other reactions are listed in Table X.

In patients receiving Neohetramine side effects were much fewer and much less severe than in the groups receiving other antihistaminics. With Neohetramine drowsiness occurred in only two cases (1.8 per cent); dryness of the mouth in one (0.9 per cent); nausea in one (0.9 per cent); and the rarer side effects were as shown in Table XII.

SUMMARY

1. The comparative toxicities and the incidence of side effects of Benadryl, Pyribenzamine, Neo-Antergan, Antistine, Histadyl and Neohetramine were studied at dosages adjusted to give equal therapeutic results in 781 allergic patients.

2. Side effects occurred with all six drugs. Drowsiness, the commonest side effect, was most frequent and pronounced with Benadryl. In contrast it occurred rarely and was least pronounced with Neohetramine. The overall incidences of side effects were as follows:

Benadryl, 61.3 per cent in 217 cases
Pyribenzamine, 35.7 per cent in 126 cases
Neo-Antergan, 24.8 per cent in 141 cases
Antistine, 22.7 per cent in 97 cases
Histadyl, 20 per cent in 89 cases
Neohetramine, 7.2 per cent in 111 cases

3. In this study of the comparative toxicity and side effects of the antihistaminic drugs, Neohetramine was found to be the least toxic in therapeutically effective doses.

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AN EVALUATION OF NEO-ANTERGAN IN DERMATOLOGY

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LOEW[7] defines an antihistaminic drug as one which is capable of diminishing or preventing several of the pharmacological effects of histamine and which does so by a mechanism other than a pharmacodynamic action diametrically opposed to that produced by histamine. Most investigators are agreed that these histamine antagonists (1) prevent histamine from increasing the permeability of capillary endothelium, thus diminishing its vasodilating action, (2) block action of the drug in the cell, (3) possibly prevent the release of histamine but have little effect on the gastrointestinal tract, blood pressure or heart in therapeutic doses.

The histamine theory, although it does not explain the sole mechanism involved in the "allergic diseases," is inferred from (1) certain similarities between anaphylaxis in animals and allergic reactions in man, and (2) the systemic effects of histamine injected artificially. Not all the symptoms in these dermatoses can be accounted for by the action of histamine, which thus explains the failure of the various antihistaminic drugs in many cases. According to Loew, failure to detect histamine blood levels does not negate the histamine theory because histamine leaves the blood stream rapidly, and extraction methods do not always detect physiologically active amounts.

Antihistaminic drugs are being clinically investigated at present because immunization by histamine or histamine conjugates (hapamine) and the inactivation of histamine by enzymes (histaminase) have been generally failures from the clinical standpoint.

The synthesis of Neo-Antergan* (pyranisamine maleate) was first reported in 1944 by Bovet and Walthert[2] in France under the label 2786 R.P. The physiological effects were described by Dews and Graham[3] in 1946 in England, and by Last and Loew[6] in this country.

Our experience has been similar to that of Arbesman[1] in regard to the comparative studies with the various antihistaminic drugs available at the present writing. Benadryl appears to be the most potent, but the frequency of side reactions, especially sedation, reduces its value in ambulatory patients. Pyribenzamine was generally valuable in cases where allergic symptoms were severe. But there are numerous cases where there is a definite place for a "less potent" antihistaminic, and Neo-Antergan seems to fill that void when other drugs have failed. As regards toxicity, there is no agreement at present among clinicians as to which drug is the least toxic but most effective agent.

Failures of antihistaminic drugs may be due to errors in diagnosis, underdosage, absence of liberated histamine in the tissues, or presence of

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*Neo-Antergan was furnished through the courtesy of Merck & Co., Inc.

other causes for the increased vascular permeability. As Lowell[8] states, there are so-called allergic diseases in which no antibodies can be demonstrated in the circulating blood or by skin testing, but which are wholly or in part caused by psychosomatic mechanisms, endocrine imbalance or nonspecific agents. The delayed effects of the antihistaminic drugs are not known at this time. The possibility of interference with the natural formation of autoantibodies in the blood and tissues remains to be seen. So far, there is no evidence that Neo-Antergan affects the antigen-antibody reaction.

DOSAGE

The dosage schedule was adjusted to the individual case. The initial dose varied from 25 to 50 mg. three times a day. Some patients with atopic eczema were given as high as 400 mg. daily, in divided doses, for four weeks. In acute urticaria most patients received 50 mg. every four hours. Children were given one-half the adult dose, although some tolerated doses of 150 mg. fairly well. In patients with intermittent symptoms, the maximum tolerated dose was taken as required. The impression was gained that patients with true allergic dermatoses could tolerate larger doses than the nonallergic group. Where itching occurred chiefly at night, the usual dosage was 100 mg. at bedtime. The longest period in which a patient was under treatment was ninety days. In those cases where there was no benefit after three weeks, or when persistent toxic side reactions appeared, the drug was discontinued and other medication prescribed.

CLINICAL STUDIES

Neo-Antergan was used in this study on 211 patients with various so-called "allergic" and nonallergic dermatoses, in order to evaluate the drug. The treatment period varied from three to ninety days. Feinberg's[4] criteria for the evaluation of antihistaminic drugs was used throughout this study, including placebo medication, discontinuance of medication to observe recurrence of symptoms, and objective improvement paralleling subjective improvement.

Clinical evaluation of an antihistaminic drug is difficult because the clinical picture may be affected by various known and unknown factors, including (1) change of physicians, (2) personality of physician, (3) psychosomatic influences, (4) seasonal influence, (5) effect of concomitant local and general therapy, (6) possibility of spontaneous cure or desensitization or remission and (7) faulty conclusions on part of patient. It is not possible to avoid these conditions in all cases, but by following Feinberg's criteria, the value of a study of this nature is increased.

In no case was there evidence of sensitization to the drug itself.

Acute Urticaria.—In sixteen cases, the results were as follows: cured seven, temporary improvement while taking the drug in seven and no

results in two. In one case of unknown etiology, a fifty mg. tablet was given every hour for eight hours without any effect on the wheals or angioneurotic edema.

Chronic Urticaria.—Hunter's[5] results with the drug in chronic urticaria were as follows: 10 per cent recurrences, 75 per cent cured and 6 per cent failures. In our series of five cases, apparent cures were obtained in four cases, with failure in one.

Papular Urticaria (prurigo simplex).—In six cases in children in which Neo-Antergan was used, relief from the pruritus was obtained in four, but there was no change in the eruption. This condition has never been proven to be an allergic dermatosis.

Penicillin Sensitivity.—In seven cases of penicillin sensitivity, we did not see any immediate results from the drug except moderate relief from the pruritus.

Exfoliative Dermatitis (secondary type).—Two cases of exfoliative dermatitis developed in patients past sixty following treatment for seborrheic dermatitis. In neither of the cases was the pruritus diminished or the eruption improved by treatment with the drug.

Pruritus Ani.—In this group were eleven cases, all of the primary psychosomatic type. In none of the cases was Neo-Antergan effective in controlling the itching. The patients had to resort to local anesthetic ointments (e.g., intracaine) to control the pruritus.

Atopic Eczema.—Control of the pruritus in this condition is "half the cure" since injury to the skin by scratching often generalizes the disorder. Although this clinical entity is called "allergic eczema," there is no proof at present that histamine is etiologic in some or any of the cases. There were twenty-five cases in this series, ten in children. The best results were in children, five with marked improvement, and moderate improvement in four. In five cases in which there was a generalized eruption, Neo-Antergan therapy was used for three months and the condition cleared, except for a residual eczema of the antecubital areas. The eczema was controlled in these cases by taking the drug when necessary to relieve the pruritus. There was no appreciable improvement in adults with this condition since there was a definite psychosomatic influence in most cases. Pruritus was not diminished until the drug was taken for at least one month. In all cases, the maximum dosage was given at night when pruritus is usually more marked. Results were negligible in two cases of asthma-eczema complex.

Disseminated Neurodermatitis.—We use this term for acute or subacute pruritic erythemas of the face, eyelids and neck and occasionally the

TABLE I. CLINICAL EFFECTS OF NEO-ANTERGAN

Diagnosis	No. of Cases	Complete Relief %	Moderate Relief %	Slight Relief %	No Relief %
Acute Urticaria	16	24	26	15	35
Chronic Urticaria	5	16	35	48	11
Atopic Eczema	25	0	65	25	10
Diss. Neurodermatitis	38	17	40	21	22
Contact Dermatitis	37	16	39	26	19
Pruritus Ani	11	0	21	65	14
Senile Eczema	16	0	25	43	32
Neurogenic Pompholyx	22	12	47	23	18
Dermatophytosis with "id" lesions	31	0	56	34	10

antecubital spaces. These are all psychomatic in origin and only affect adults, especially women thirty to fifty. In thirty-eight cases in which the drug was prescribed for three-week periods, there was no appreciable change in the pruritus or clinical picture. In twenty-two cases in this group, none were improved by Neo-Antergan; sixteen reported slight relief from the intolerate itching. Mild sedation, simple psychotherapy, intravenous calcium and local soothing lotions were most effective.

Contact Dermatitis (subacute and chronic).—We used the drug in a group of thirty-two cases, not only for its antipruritic action, but to observe its ability, if any, to prevent autosensitization. In six cases, the drug did not prevent generalized spread of the eruption. It is possible that the drug was not used in large enough doses in these cases for the full antihistaminic effect to be evident. The pruritus of poison ivy dermatitis was satisfactorily controlled in nine cases, although local therapy was also used.

Nummular Eczema.—In four cases in which the drug was used, there was no change in the lesions or pruritus. This was expected since the cause of this dermatosis is undetermined.

Post-Scabetic Dermatitis.—In twelve cases in which contact dermatitis and reinfection were ruled out, good results were obtained for all.

Dermatitis Herpetiformis.—In two cases where the drug was used for three weeks, there was no effect on the eruption or pruritus until sulfapyridine was substituted. It is apparent that antihistaminics are not indicated in this disease.

Erythema Multiforme.—In four cases of the recurrent idiopathic type, no subjective or objective improvement occurred after three weeks. In one case, an attack was not aborted although the patient had been taking the drug for four weeks.

SIDE REACTIONS

Toxic reactions were mild, transient in most cases and unpredictable. The percentage of side reactions (19 per cent with Neo-Antergan) was extremely low even when a total of 400 mg. was given daily. Moderately toxic symptoms occurred in ten patients, mild side reactions in thirty-two.

The most frequent complaint was nausea. In thirteen per cent of the cases, the patients could not tolerate Pyribenzamine either and complained of insomnia, a "jumpy feeling" in the legs, numbness and vomiting, with both drugs. Symptoms complained of, in order of frequency, were as follows:

	Number Cases
Nausea	14
Dizziness	6
Paresthesias	5
Nervousness	3
Insomnia	3
Weakness	3
Headache	2
Cramps (gastrointestinal)	2
Heartburn	2

CONCLUSIONS

1. Neo-Antergan is useful in certain types of "allergic" dermatoses.

2. Its toxicity is relatively low. Its depressant action is much less than Benadryl.

3. A marked difference in response to the drug is apparent in different cases of the same disease.

4. There was no accumulative action, no evidence of habit formation and no effect on the blood pressure, heart or hemogram in thirty cases investigated.

5. Elimination of the causative agent, desensitization where possible, attention to psychosomatic factors and proper local therapy are considered more important than antihistaminic drugs in their present state of development.

6. Failures were believed to be caused by inadequate dosage, improper timing of dosage or absence of liberated histamine in the tissues.

7. Diagnostic tests with antihistaminic drugs are not reliable since many conditions which are definitely nonallergic may clear up as a result of other factors.

8. The indiscriminate use of antihistaminic drugs as a substitute for a careful history, physical examination and prolonged period of observation is to be condemned.

9. If the physician will learn not to expect too much from an antihistaminic drug, Neo-Antergan should be useful in the "allergic dermatoses" as supplementary therapy.

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SUBCUTANEOUS EMPHYSEMA COMPLICATING CHRONIC BRONCHIAL ASTHMA

Report of Two Cases

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SUBCUTANEOUS emphysema complicating bronchial asthma is comparatively rare. In 1945, Schwartz[5] reviewed twenty-six cases reported in the literature. In all of the reported cases the patients recovered on conservative treatment, with the exception of one, in whom multiple neck incisions were performed to permit the air to escape. They were all characterized by cyanosis, dyspnea, subcutaneous swelling of the neck and adjacent parts of the body. Two cases herein reported are similar and the patients made uneventful recoveries. In the second case, however, there was a very extensive involvement of the face, neck, thorax (anterior and posterior), the abdomen, the upper part of the back and the right inguinal region (patient complained of pain a few hours before it appeared).

Extreme pulmonary distention is common during attacks of asthma. There may be a marked narrowing of the lumina of the smaller bronchi. The obstruction is caused by a spasm of the bronchial muscles and in part by a swelling of the mucous membrane with an accumulation of exudate in the lumen of the bronchi. During inspiration the pressure in the thoracic cavity lessens, thus widening the alveoli and bronchioles and permitting air to enter the narrowed passages. With expiration, however, the pressure in the thoracic cavity rises; this tends to lessen the diameter of the bronchioles, and since they are already constricted, collapse ensues. The rupture takes place in the apices and along the mediastinal margins where there is no bony support. Air migrates through the tissues into the mediastinum and neck and may extend to the thorax.

*Case 1.**—I. M., a girl, aged fifteen years, was admitted to St. Joseph's Hospital on November 15, 1947, with the chief complaint of swelling of the neck.

Past History: At the age of five months, the patient was admitted to St. Joseph's Hospital with lobar pneumonia. She made an uneventful recovery. Three months later (eight months of age), she commenced her asthma attacks. At the age of three she was readmitted to the hospital (December 12, 1935) with a diagnosis of asthma. She was discharged on January 5, 1936. During her residency in the hospital, the laboratory examinations revealed the urine to be negative. Blood findings revealed: leukocytes, 8,200; small lymphocytes, 22 per cent; large lymphocytes, 38 per cent; large mononuclear cells, 4 per cent; polymorphonuclear leukocytes, 35 per cent, and eosinophils, 1 per cent. Treatment consisted of an elimination diet and supportive symptomatic measures. The next admission was on November 17, 1937, when, following a cold, she developed asthma. Laboratory examinations showed: hemoglobin, 70 per cent; erythrocytes, 4,260,000; leukocytes, 13,000; small lymphocytes, 8 per cent; large lymphocytes, 17 per cent; large mononuclear cells, 1 per cent; polymorphonuclear leukocytes, 74 per cent; urine—albumin, 1-plus; sugar,

*From the medical service of James E. Phelps, M.D., attending physician in medicine at St. Joseph's Hospital, Paterson, New Jersey.

3-plus, and few pus cells. Repeated urinalysis showed completely negative results. The vaginal smear was negative for pathogenic organisms. She was discharged as improved on November 21, 1937. She came under our observation during the attack of subcutaneous emphysema on November 16, 1947. After her release from the hospital, skin tests were performed and positive reactions noted to many inhalants, ragweed pollens and a few foods. She was placed on an elimination diet, and injection —therapy to ragweed pollens and mixed inhalants was begun. She recovered from the asthma and has attended school regularly since then.

Present History: An attack of asthma began on November 14, 1947, and the next morning at 3:00 a.m. she was suddenly awakened by pain on the right side of the neck; a few hours later, it extended to both sides of the neck and the laryngeal region. She also had coughing, accompanied by pain in the area of the right suprasternal notch. Examination revealed a swelling of the neck, more on the right side, with crepitation in both supraclavicular areas. A few wheezes were present throughout the anterior and posterior regions of the chest. An x-ray examination on November 17, 1947, was negative in both the pulmonic field and the central heart shadow. Laboratory examinations revealed the Kahn reactions to be negative; urine, negative; hemoglobin, 14.5 gm. or 85 per cent; erythrocytes, 4,350,000; leukocytes, 9,700; small lymphocytes, 16 per cent; monocytes, 7 per cent; large mononuclear cells, 2 per cent; neutrophils, 73 per cent, and non-segmented cells, 2 per cent.

Case 2.—The second case was that of an extensive subcutaneous emphysema in a twenty-two-year-old man.

Past History: Asthma began at the age of eight years following an attack of scarlet fever, and it became worse at the age of thirteen, especially in the summertime. In March, 1941, he was found sensitive to pollens, inhalants and some foods.

Present History: Severe asthma followed an upper respiratory infection which began on December 18, 1948. He had not responded to the usual methods of treatment.

Diagnosis and Therapy: Bronchial asthma, vasomotor rhinitis and pollen asthma. He was placed on an anti-asthmatic diet, with environmental restrictions, and was instructed as to the use of allergen-proof material over the bedding. Injections with pollens, dust and the special inhalants were given regularly. He was observed uninterruptedly until 1944 when he discontinued treatment. He continued to remain free of asthma, although occasionally (four to six times a year) he had some wheezing which was relieved by 0.3 to 0.5 c.c. of suprarenalin in gelatin subcutaneously.

Although aminophylline, grains 7¾, was given intraveonusly, the cough persisted; he was dyspneic, and marked wheezing was evident over the anterior and posterior aspects of his chest. Three hours later, 2 grams of sodium iodide were administered intravenously, and 1 c.c. of suprarenalin in gelatin was injected subcutaneously since he had been previously helped by this procedure. Relief was obtained but it was of short duration. Three hours later, 50 c.c. of 50 per cent glucose were given intravenously and 0.5 c.c. of suprarenalin in gelation was injected subcutaneously. Three hours later, aminophylline, 7¾ grains, was added intravenously and 0.5 c.c. suprarenalin in gelatin subcutaneously. He expectorated a very thick and tenacious, occasionally blood-streaked, sputum throughout most of the night. The next day, the asthma was somewhat relieved; there was less dyspnea with some expectoration. After 50 c.c. of 50 per cent glucose, intravenously, and 0.5 c.c. of suprarenalin in gelatin, subcutaneously, were given, he had a fair day, but coughed almost continuously. The following day he complained of tightness of his throat, and swelling of the neck and face. There was crepitation on digital pressure over the neck, lower

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ANXIETY AS A FACTOR IN ASTHMA

A Case Report

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IN THE PAST few years, allergists have become more conscious of the part played by the psyche in the production and aggravation of the symptoms of asthma. Psychotherapy has produced spectacular results in many stubborn cases of bronchial asthma which have resisted all types of immunization procedures. The following case report shows how well anxiety may affect the course of asthma. The treatment of this patient combined a drastic surgical procedure with a psychosomatic approach.

CASE REPORT

R.E., a nineteen-year-old white man, was first seen with a history of three years of repeated asthmatic attacks. In January, 1945, after two months in the Navy, he was discharged because of a right-sided hernia and bronchial asthma. The bronchial asthma became worse following his discharge, and he was placed in a Naval hospital in California for twenty-three days. During his stay there, a Navy surgeon told him that he had only two years to live. From that time on, he was constantly in fear of his life. He was hospitalized three times before we saw him on April 21, 1947.

His past history was negative except for a right herniorrhaphy done in 1947 and an appendectomy in 1932. His family history showed asthma in a paternal great-grandfather.

Physical examination was essentially negative except for a pale, boggy, nasal mucous membrane, and a few râles throughout the lung fields.

Laboratory and x-ray procedures were negative. Skin tests showed marked intradermal reactions to house dust, feathers, and Alternaria.

Treatment was instituted with immunization and precautions to house dust and Alternaria. This regime brought fairly good results. The patient, for the first time, seemed to think that he was being helped. His confidence increased greatly as the months went by. His first hospitalization under our care was brought about when he found out that I was to be away for three days. When I returned from my trip, I was greeted with a peculiar picture of a steam-engine puffing type of respiration, which was not relieved by epinephrine (1:1000). Heavy sedation finally brought him back to normal.

Five months later he developed influenza associated with an increase of the bronchial asthma. The infection finally cleared with antibiotic treatment, but his asthma gradually became worse. He was hospitalized for the second time. On his second day of hospitalization, his condition became critical. Every known anti-asthmatic procedure was attempted, including intravenous 5 per cent ethyl alcohol, intravenous glucose and aminophylline, helium, oxygen, ether-in-oil by rectum, and sedation. Within an hour three bronchoscopists refused to bronchoscope my patient because of his severe asthmatic state. Large doses of intramuscular sodium phenobarbital gave him momentary rest, but he soon became cyanotic and his pulse became too fast to be counted. Death seemed only a few minutes away. An otolaryngologist was called, and he immediately performed a tracheotomy at my insistence. The patient quieted down after mucus was aspirated from his trachea. His course in the hospital was uneventful from that day.

My surgical colleague and I agreed that this patient should have psychotherapy since it became evident from conversation with the patient that he had a serious anxiety neurosis, manifesting itself by a marked fear of death.

The patient refused psychoanalysis, but in discussing his condition with him in three visits of a half hour each, I found that the Navy surgeon had produced this fear of death with the words "you only have two years to live." When I reminded him that we always have tracheotomy available for him to breathe, if necessary, he seemed to lose most of his fear. Then after I mentioned that he had outlived the two-year prediction, I knew that his fear would vanish. His asthma has never recurred since this last attack in November, 1947.

DISCUSSION

In commenting about this case, I wish to state that extreme circumstances of this sort would not have occurred in a normally adjusted person. Such a person would not have been satisfied with this two-year ultimatum and would have sought more expert advice. This young man was not normally adjusted, as I found out from questioning his parents and friends. As a boy, he had no playmates, read books continually, and was a steady companion of his grandmother. In adolescence, he was rather chubby and would not participate in games or sports. He shunned the opposite sex. When his asthma began, he became more conscious of being different from other boys, and this added to his maladjustment. In order to prove his masculinity, he joined the Navy in December, 1945, but his discharge, two months later, left him with a severe depression. The final blow, which produced the anxiety neurosis, was struck by the Navy surgeon. Today, he has not only lost his asthma, but he is adjusting himself well to his environment. How long this will last no one knows, since these maladjusted individuals tend to revert to their former state under an adverse turn of circumstances.

SUMMARY

1. A case report has been presented in which anxiety was a major factor in the causation of asthma.

2. Tracheotomy was used as a life-saving measure in this case, in which the condition was chiefly precipitated by anxiety.

3. It is suggested that psychosomatic concepts be considered in all cases of asthma, so that these patients may be treated more effectively.

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SCHOLARSHIP AWARDS

The American College of Allergists wishes to acknowledge its thanks to the following firms for making it possible to give eight scholarships at the postgraduate instructional course in allergy given under the auspices of Baylor University College of Medicine, Houston, Texas, October 31 through November 5, 1949. The firms are: Allergen-Proof Encasings, Inc., The DeVilbiss Company, Hoffmann-La Roche, Inc., Hollister-Stier Laboratories, Luzier's Inc., Marcelle Cosmetics, Inc., Nepera Chemical Co., Inc., Rexair Division, Martin-Parry Corporation, and Schering Corporation.

POLLEN ALLERGY IN THE CITY OF SAO PAULO, BRAZIL

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São Paulo is the second city of Brazil, the third largest of all South America, with a population of 1,400,000 inhabitants. A large part of the population are Italian, Portuguese, Arabian, Japanese, Spanish, and German, or descendants of these people. Therefore, those who previously lived elsewhere had the opportunity of acquiring sensitivity to pollens in their respective countries.

The first contribution to the study of pollen allergy in the city of São Paulo was presented by the author.[2] This consisted of a study and classification of the plants which are capable of causing pollen allergy, including their time of pollination. This was followed by a preliminary report[3] which showed the incidence of air-borne pollen, correlated with the meteorologic conditions and the number of postive skin reactions to pollens in Brazilian people. These results were confirmed by Oliveira Lima et al,[1] with the exception that they did not note the pollen of the eucalyptus. Later the author studied the causes of the rarity of pollen allergy in Brazil.

As a result of these observations the following conclusions in allergy in Brazil, particularly in the city of São Paulo, were reached:

1. Pollen allergy is rarely observed in Brazil, particularly in the city of São Paulo.
2. The Brazilian people are not constitutionally refractory to pollen allergy.
3. Brazilian people are able to acquire pollen allergy when they locate in countries where pollenosis is found.
4. The family history of allergic patients born in Brazil with foreign ancestors may show cases of pollen allergy in parents, grandparents or uncles and aunts.
5. The rarity of pollen allergy depends mainly on the environmental factors.
6. Patients suffering with pollenosis from other countries were relieved of symptoms while living in Brazil.
7. The same race that usually develops pollen allergy in the United States does not develop the disease in Brazil (Japanese, et cetera).
8. The following plants, the pollen of which is capable of causing pollenosis in other countries, were noted in Brazil: *Cynodon dactylon, Pao annua, Chenopodium ambrosioides, Polygonum acre, Rumex crispus* and the genus *Ambrosia (Ambrosia polystachya).*
9. Those who suffered hay fever in other countries gave positive skin reactions to extracts of the same pollens noted in Brazil (see below).
10. Hay fever patients, sensitized to European grass pollen, showed positive skin reactions with extracts from Brazilian grass *(Cynodon dactylon* and *Melinis minutiflora).* The same is observed with allergic pa-

tients sensitized to North American ragweed *(A. artemisiaefolia* and *A. elatior)*. They react in the same way to native Brazilian ragweed *(Ambrosia polystachya)*.

11. The air-borne pollens of major clinical significance in Brazil are: *Chenopodium ambrosioides, Amaranthus spinosus, Cynodon dactylon,* and *Poa annua*. The genus Ambrosia is represented in Brazil by the species *A. polystachya*.

12. The air-borne pollens with minor hay-fever-producing substance are: *Xanthium sponsum, Rumex crispus, Morus alba, Morus migra* and the genus Platanus. Eucalyptus is also included; it is insect borne.

13. The air-borne pollens of unknown or questionable cause of hay fever, occurring in great quantity are: *Melinis minutiflora* (forage grass), and *Parthenium hysterophorus*. The latter was found only in the city of *São Paulo*.

14. Plants of the genera Ambrosia, Amaranthus, and Chenopodium and the grasses *Cynodon dactylon* and *Poa annua* are not found in great quantity.

15. The maximum pollen count in the city of São Paulo per 2 sq. cm. was as follows: *Parthenium hysterophorus,* 42; *Melinis minutiflora,* 40; *Cynodon dactylon,* 15; and *Amaranthus sp.,* 15.

16. The low incidence of pollen allergy in Brazil is obviously the result of the scarcity of hay-fever-producing pollens.

17. Pollen of *Eucalyptus sp.* is only found in large quantities (maximum 100 per 2 sq. cm.) near great plantations and does not have a potent exciting substance causing allergy.

18. There are only three plants *(Eucalyptus sp., Parthenium hysterophorus* and *Melinis minutiflora)* whose pollen concentration is capable of producing hay fever in the city of São Paulo.

19. The pollen of *Parthenium hysterophorus* and *Melinis minutiflora* are probably without potent hay fever substance. The concentration of the latter is fairly constant at certain times in May and June.

20. The pollen of *Melinis multiflora* was in sufficient concentration to produce hay fever in a patient previously sensitive to the grass pollen of a foreign country.

21. The time of pollination of most Brazilian plants of allergic significance is during the rainy season, September to March. The incidence during this period is not great.

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UNUSUALLY GOOD RESULTS IN POLLINOSIS WITH COMBINED ANTIGEN-ANTIHISTAMINE THERAPY, SHORTENING THE TREATMENT OF HAY FEVER

Study I

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THE INTRODUCTION of antihistaminic drugs has given a new impetus to the treatment of allergic diseases. In the past, these drugs primarily have been employed for symptomatic relief, and numerous reports have appeared in the literature attesting their palliative effectiveness.

The possibility that antihistaminic preparations can assume a major role in hyposensitization therapy has received scant attention. Arbesman and his associates[1] studied eight patients in whom repeated constitutional reactions, incurred in the course of routine hyposensitization therapy, were prevented by a preliminary dose of 100 mg. of Pyribenzamine. They also observed one patient who could tolerate, without reaction, 50 per cent more allergen than formerly when a preliminary dose of Pyribenzamine was given. Fuchs et al[2] reported that 50 mg. of Pyribenzamine, administered prior to the injection of pollen antigen, made possible greater dosage increases of pollen extract in twenty-six cases, and that their patients were able to reach a maximum dosage almost twice the amount they usually tolerated when taking the pollen extract alone. Green[3] found effective, in permitting the administration of larger amounts of antigen, 25 mg. of Pyribenzamine, administered prior to pollen therapy in hypersensitive patients, and observed no constitutional reactions when the effect of the antihistaminic agent had been dissipated.

The purpose of this paper is to present a new concept in pollen therapy. It essentially embodies the administration of large, rapidly increasing hyposensitization doses of pollen antigen, made possible by a twenty-four-hour simultaneous administration orally of a suitable antihistaminic preparation with each injection. The integration of these two therapeutic measures decidedly shortens the length of treatment in pollen allergy, decreases the number of injections, safely allows the administration of larger individual doses and more adequate total amounts of pollen antigen, and produces more uniformly satisfactory results.

RATIONALE OF COMBINED HYPOSENSITIZATION-ANTIHISTAMINIC THERAPY

Massive doses of pollen antigen, such as are about to be described, ordinarily would likely precipitate a severe constitutional reaction. However, a patient, protected with an antihistaminic agent, can tolerate repeatedly large, progressively increasing, provocative or shock doses of pollen antigen. From clinical results obtained in our study of a limited number of

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private patients, it appears that antihistaminic preparations "inactivate or neutralize" some "general-reaction-producing-substance," probably closely allied to histamine or H-substance, released locally by the excessive dose of antigen, which, without effective antihistaminic protection, would seriously shock the patient. Antihistaminic medication, administered in adequate amounts, exerts a prophylactic influence against the anticipated constitutional reaction of a deliberate overdose of pollen antigen. It further appears that the "inactivation or neutralization" of this "general-reaction-producing substance" by antihistaminic agents does not inhibit the formation of protective or blocking antibodies.

POLLEN DOSAGE SCHEDULE

Preseasonal and coseasonal pollen dosage schedules, which were both practical and rapid, were formulated. A maintenance schedule, designed to preclude subsequent preseasonal or coseasonal therapy, was also devised for perennial treatment. The doses were further arranged according to weight —for patients 100 pounds and over and for those under 100 pounds. The dose of the pollen extract, with its anticipated local release of a "general-reaction-producing substance," was governed not by the degree of response of the patient but by the amount of antihistaminic medication ("inactivating or protective" agent) which, in turn, depended upon the patient's weight.

The pollen unit dose employed in developing the schedule was the Coca-Noon Pollen Unit (0.00001 mg. of total nitrogen). In treating our patients, the allergenic extracts* of mixed grasses (20,000 pollen units per c.c., composed of equal parts of the pollens of June grass, orchard grass, sweet vernal grass, redtop, and timothy) and ragweed combined (20,000 pollen units per c.c., composed of equal parts of the pollens of common and giant ragweeds) were employed. Fresh extract was obtained every two to four weeks and was administered well in advance of the expiration date.

The pollen dosage schedule has been formulated for Boston, Massachusetts, and surrounding communities where the grass season of the most common and principal offenders (June grass, orchard grass, sweet vernal grass, redtop, and timothy) approximately extends from May 15 to July 15 and the ragweed season from about August 15 to September 20 or October 1. However, during the 1948 season in the Boston area, the grass season extended into September and ragweed pollen was still in the air up to November 15. The pollen dosage schedule, with slight variations in timing, can easily be employed in other sections of the country.

Preseasonal Schedule.—The preseasonal schedule (Table I) consists of eight rapidly increasing doses of pollen antigen which are arranged according to the weight of the patient. Those 100 pounds or over received a

*Prepared by the Lederle Laboratories, Pearl River, N. Y.

TABLE I. POLLEN DOSAGE SCHEDULE

Visit	Preseasonal		Coseasonal		Perennial	
	Patients 100 pounds and over	Patients under 100 pounds	Patients 100 pounds and over	Patients under 100 pounds	Patients 100 pounds and over	Patients under 100 pounds
1	250 PU	125 PU	125 PU	65 PU		
2	500 PU	250 PU	250 PU	125 PU		
3	1,250 PU	625 PU	625 PU	310 PU	20,000 PU	10,000 PU
4	3,000 PU	1,500 PU	1,500 PU	750 PU	bimonthly	bimonthly.
5	6,000 PU	3,000 PU	3,000 PU	1,500 PU	6 injections	6 injections
6	10,000 PU	5,000 PU	5,000 PU	2,500 PU	per year.	per year.
7	15,000 PU	7,500 PU	7,500 PU	3,750 PU		
8	20,000 PU	10,000 PU	10,000 PU	5,000 PU		
Total	56,000 PU	28,000 PU	28,000 PU	14,000 PU	120,000 PU	60,000 PU

preseasonal total of 56,000 Coca-Noon Pollen Units (250, 500, 1,250, 3,000, 6,000, 10,000, 15,000, and 20,000); while patients under 100 pounds were given a preseasonal total of 28,000 units (125, 250, 625, 1,500, 3,000, 5,000, 7,500, and 10,000).

Preseasonal treatment was instituted at any time. Hyposensitization injections were given monthly, biweekly, weekly, or semiweekly. For each patient, the schedule of injections was predetermined, in order that the eighth dose would be administered just prior to the inception of the pollen season. There were thirty-seven patients on preseasonal ragweed therapy; fourteen received injections monthly, five biweekly, seventeen weekly, and one semiweekly. Six of these thirty-seven patients were simultaneously receiving coseasonal grass treatments also.

Coseasonal Schedule.—The coseasonal schedule (Table I) consists of eight progressively increasing doses of pollen antigen. Injections were administered weekly. Patients 100 pounds and over received a total of 28,000 Coca-Noon Pollen Units in divided doses (125, 250, 625, 1,500, 3,000, 5,000, 7,500, and 10,000 units); those under 100 pounds were given a total of 14,000 units (65, 125, 310, 750, 1,500, 2,500, 3,750, and 5,000). Fourteen patients received coseasonal therapy; four ragweed and ten grass. Six of the latter simultaneously received preseasonal ragweed injections also.

If the pollen season is longer than eight weeks, the eighth dose can be repeated weekly until the season ends. With a shorter season, as many coseasonal weekly injections as possible should be administered, the balance of the schedule then can be completed postseasonally and merged into the maintenance phase of specific pollen therapy.

When preseasonal therapy was instituted late, the preseasonal schedule of doses was administered until the specific season began, at which time the pollen unit dose was switched to a corresponding level in the coseasonal schedule. Injections were administered weekly until the top coseasonal dose was attained. The latter was continued weekly until the season ended.

Perennial Schedule.—The perennial schedule (Table I) extends from the end of one season to the beginning of the next and is continued for several years. It consists of the administration of top pollen doses at bimonthly intervals beginning with the month immediately following the

TABLE II. DISTRIBUTION OF ANTIHISTAMINIC DRUGS IN FORTY-FIVE CASES OF POLLEN SENSITIVITY

Antihistaminic Drug	No. of Pollen Cases	Grass	Ragweed	Combined Grass and Ragweed
Pyribenzamine Hydrochloride	5	1	3	1
Benadryl Hydrochloride	5		4	1
Histadyl Hydrochloride	5	2	3	
Thephorin	14	1	12	1
Neo-Antergan Maleate	6		4	2
Tagathen	3		3	
Decapryn Succinate	3		3	
Hydryllin	1			1
Thenylene Hydrochloride	1		1	
Neohetramine	2		2	
Total	45	4	35	6

season. The last (sixth) perennial dose should be given just before the next season begins. Thus, with six bimonthly injections given yearly, the need of subsequent preseasonal or coseasonal therapy is obviated.

The maintenance dose for patients 100 pounds and over is 20,000 Coca-Noon Pollen Units. This dose is injected bimonthly—a total administration of 120,000 units per year. The maintenance dose for those under 100 pounds is 10,000 pollen units given bimonthly—a yearly total of 60,000 units. Each year, the first and sixth doses should be respectively injected immediately after one season and before the next.

In all coseasonal patients, the coseasonal top dose was merged into the perennial schedule by one intermediate monthly injection. According to the patient's weight, the last coseasonal doses (eighth) were increased to 15,000 and 7,500 units the month immediately following the season. The next month they were increased to the top maintenance dose of the perennial schedule.

ADMINISTRATION OF ANTIHISTAMINIC DRUGS

In our study, the following antihistaminic drugs were employed: (1) Pyribenzamine Hydrochloride, (2) Benadryl Hydrochloride, (3) Histadyl Hydrochloride, (4) Thephorin, (5) Neo-Antergan Maleate, (6) Tagathen, (7) Decapryn Succinate, (8) Hydryllin, (9) Thenylene Hydrochloride, and (10) Neohetramine. Histadyl Hydrochloride and Thenylene Hydrochloride have the same chemical formula. These antihistaminic preparations were administered orally, in conjunction with hyposensitiza-

TABLE III. DOSAGE OF ANTIHISTAMINIC DRUGS

Antihistaminic Drug	Pre-injection Dose	1st Post-injection Dose	2nd Post-injection Dose*	3rd Post-injection Dose*	4th Post-injection Dose	5th Post-injection Dose	Total
Pyribenzamine Hydrochloride	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Benadryl Hydrochloride	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Histadyl Hydrochloride	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Thephorin	50 mg.	50 mg.	25 mg.	25 mg.	25 mg.	25 mg.	200 mg.
Neo-Antergan Maleate	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Tagathen	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Decapryn Succinate	50 mg.	50 mg.	25 mg.	25 mg.	25 mg.	25 mg.	200 mg.
Hydryllin	50 mg.	50 mg.	25 mg.	25 mg.	25 mg.	25 mg.	200 mg.
Thenylene Hydrochloride	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.
Neohetramine	100 mg.	100 mg.	50 mg.	50 mg.	50 mg.	50 mg.	400 mg.

*When the pollen antigen was administered late in the afternoon, the second and third post-injection doses were combined and given as a double dose at bedtime.

TABLE IV. ANTIHISTAMINIC ADMINISTRATION SCHEDULE

	20 minutes	1 hour	4 hours	4 hours			
	Pre-injection Double Dose of Anti-histaminic	Pollen Antigen Injection	1st Post-injection Double Dose of Anti-histaminic	2nd Post-injection Single Dose of Anti-histaminic	3rd Post-injection Single Dose of Anti-histaminic	4th Post-injection Single Dose of Anti-histaminic	5th Post-injection Single Dose of Anti-histaminic
Pollen antigen administered in the morning	9:40 a.m.	10 a.m.	11 a.m.	3 p.m.	7 p.m.	11 p.m.	7 a.m.
Pollen antigen administered in early afternoon	1:40 p.m.	2 p.m.	3 p.m.	7 p.m.	11 p.m.	7 a.m.	12 noon
Pollen antigen administered in late afternoon	5:40 p.m.	6 p.m.	7 p.m.	11 p.m. (2nd and 3rd post-injection doses combined)		7 a.m.	12 noon

tion therapy, to forty-five pollen-sensitive patients; four grass, thirty-five ragweed, and six combined (Table II). Throughout the study, the patients always received the antihistaminic drug originally allotted to them.

Both the individual doses and total twenty-four-hour administration were large—about two and one-half times the recommended amounts. Doses were given according to the patient's weight. Patients 100 pounds and over received doses as tabulated in Table III; those under 100 pounds received 50 per cent less.

Antihistaminics were administered prophylactically in such a manner that their effect lasted for about twenty-four hours (Table IV). A preliminary double dose (preinjection dose) was given twenty minutes prior to each injection of pollen antigen. One hour after the injection, the patient received another double dose (first postinjection dose). Thereafter, a single dose was administered every four or five hours for four doses (second, third, fourth, and fifth postinjection doses). When the pollen extract was given late in the afternoon, the second and third postinjection doses were combined and administered as a double dose at bedtime.

TABLE V. SIDE REACTIONS TO LARGE DOSES OF ANTIHISTAMINIC DRUGS DURING A TWENTY-FOUR-HOUR PERIOD

Patients coded by case number (Table VII).

Antihistaminic Drug	No. of Patients Receiving Antihistaminic Drug	No. of Patients with Side Reactions	Drowsiness	Nausea	Dizziness	Numbness	Fatigue	Insomnia
Pyribenzamine Hydrochloride	5	4	18,27,36,39	18,27,36,39	39			
Benadryl Hydrochloride	5	4	30,31,35,37					
Histadyl Hydrochloride	5	4	19,23,26,40					
Thephorin	14	5	3, 7, 12, 17				17	25
Neo-Antergan Maleate	6	3	6, 8, 9					
Tagathen	3	3	32, 33, 34					
Decapryn Succinate	3	1	20			20		
Hydryllin	1	1	13					
Thenylene Hydrochloride	1	1	38	38	38			
Neohetramine	2	1	28					

In twenty-seven patients (60 per cent), side reactions were encountered to all the antihistaminic drugs employed (Table V). Despite the large doses, side effects were relatively mild and were never severe enough to warrant discontinuance of the drug. Drowsiness was the most frequent and prominent side effect. Nausea, dizziness, numbness, fatigue, and insomnia occasionally occurred also. In the majority of the cases, early side reactions either disappeared or were greatly diminished with continued administration.

CONSTITUTIONAL REACTIONS

As a prognosticator, the local reaction following the subcutaneous administration of pollen antigen was not dependable in foretelling the occurrence of a constitutional reaction. Mild, generalized symptoms were encountered with both small and extensive local reactions.

In our study of forty-five pollen-sensitive patients, seven patients (six preseasonal ragweed and one coseasonal grass) developed slight systemic symptoms. This represents seven constitutional reactions out of 360 treatment visits (1.6 per cent). There were no generalized reactions in the combined grass-ragweed sensitive patients. Sneezing, pruritus, urticaria, angioneurotic edema, and asthma were noted. These symptoms were delayed, occurring from one to twelve hours after the injection and lasted from a few minutes to four hours, being readily controlled with additional postinjection oral doses of an antihistaminic medication.

Whenever a constitutional reaction was encountered, however insignificant, the remaining pollen dosage schedule was reduced by 50 per cent. Despite this reduction, these exquisitely sensitive patients received in eight injections a total pollen dosage far in excess of the amount they could have tolerated without antihistaminic agents. After the specific season, begin-

TABLE VI. TWO YEAR COMPARISON OF PRESEASONAL RAGWEED TOTAL POLLEN DOSAGE IN NINE PATIENTS

Case No.	Weight	Age	1947 Total Pollen Dosage	1948 Total Pollen Dosage with Antihistaminic Integration	Times Pollen Units Increased	Antihistaminic Drug
2—B.N.	125 lbs.	50 yrs.	14,600 PU	56,000 PU	3.8	Thephorin
3—C.B.	170 lbs.	53 yrs.	4,100 PU	56,000 PU	13.6	Thephorin
4—H.W.	115 lbs.	27 yrs.	2,100 PU	56,000 PU	26.6	Thephorin
5—J.D.	65 lbs.	8 yrs.	9,145 PU	28,000 PU	3	Neo-Antergan
6—N.C.	130 lbs.	27 yrs.	12,000 PU	56,000 PU	4.7	Neo-Antergan
10—P.G.	135 lbs.	32 yrs.	10,800 PU	56,000 PU	5.1	Neo-Antergan
21—P.L.	130 lbs.	35 yrs.	2,850 PU	56,000 PU	19.6	Decapryn Succinate
22—E.L.	140 lbs.	34 yrs.	6,695 PU	56,000 PU	8.3	Decapryn Succinate
25—D.B.	120 lbs.	30 yrs.	10,250 PU	56,000 PU	5.4	Thephorin

ning with the first bimonthly perennial injection, the pollen dose was increased by 2,500 pollen units with each treatment until the top maintenance dose of 20,000 pollen units was attained. The latter was repeated bimonthly as suggested in the perennial schedule.

RESULTS

Forty-five pollen-sensitive patients (four grass, thirty-five ragweed, and six combined) from private practice received the combined hyposensitization-antihistaminic therapy. Injections were given subcutaneously in the arm. There were twenty-four females and twenty-one males. Forty-one patients were over 100 pounds; four were less than 100 pounds. Their ages ranged from eight to fifty-six years.

Clinical sensitivity was determined by the history and scratch tests performed with an extract of a 1-50 dilution. By skin tests, these patients had no associated sensitivities to foods, house dust, or moulds. Besides the six combined cases, eighteen of the thirty-five clinically sensitive ragweed patients also exhibited positive skin reactions to grass. These, however, lacked a positive clinical history, were considered "latent" cases, and did not receive grass hyposensitization therapy.

All the patients remained in the Greater Boston area during their specific season. None lived or were employed in air-conditioned establishments. All pursued their normal, daily routine. No medication was administered to the preseasonal cases during their specific season. The coseasonal patients received antihistaminic agents for twenty-four hours only with each weekly coseasonal pollen injection as per schedule.

Postseasonal serial testing of the skin and conjunctiva was not done. Results were based on the clinical course. Each patient kept his own clinical diary and carefully recorded the appearance and duration of any symptom. Results were tabulated as follows: 100 per cent, completely symptom-free; 95 per cent, a few sneezes accompanied with an insignificant and fleeting nasal obstruction; 75 per cent, slight symptoms lasting from two to four days during the height of the season; and 50 per cent slight to moder-

TABLE VII. RESULTS OF COMBINED HYPOSENSITIZATION-ANTIHISTAMINIC THERAPY IN FORTY-FIVE POLLEN SENSITIVE PATIENTS

Case No.	Age and Sex	Lbs.	Injections Given	Antihistaminic Drug	Total Cosea-sonal Grass PU	Total Cosea-sonal Ragweed PU	Total Presea-sonal Ragweed PU	Total PU Given	Consti-tutional Reaction	Clinical Result
1 N.K.	47 F	165	monthly	Thephorin	0	0	38,500	38,500	1 with 10,000 PU dose	100%
2 B.N.	50 M	125	monthly	Thephorin	0	0	56,000	56,000	none	100%
3 C.B.	53 F	170	monthly	Thephorin	0	0	56,000	56,000	none	100%
4 H.W.	27 M	115	monthly	Thephorin	0	0	56,000	56,000	none	100%
5 J.D.	8 M	65	monthly	Neo-Antergan	0	0	28,000	28,000	none	100%
6 N.C.	27 F	130	Grass weekly Ragweed monthly	*Neo-Antergan	28,000	0	56,000	84,000	none	100%
7 C.M.	36 M	170	Grass weekly Ragweed monthly	*Thephorin	28,000	0	56,000	84,000	none	100%
8 J.D.	37 M	170	monthly	*Neo-Antergan	0	0	56,000	56,000	none	100%
9 L.E.	33 F	140	monthly	*Neo-Antergan	0	0	56,000	56,000	none	100%
10 P.G.	32 F	135	monthly	Neo-Antergan	0	0	56,000	56,000	none	100%
11 W.K.	56 M	180	weekly	Thephorin	28,000	0	0	28,000	none	100%
12 J.M.	25 F	120	weekly	*Thephorin	0	0	29,000	29,000	1 with 1,250 PU dose	100%
13 D.M.	12 F	110	weekly	*Hydryllin	28,000	0	56,000	84,000	none	Grass 100% Ragweed 75%
14 E.W.	13 F	115	Grass weekly Ragweed monthly	Neo-Antergan	28,000	0	56,000	84,000	none	100%
15 F.A.	30 F	115	monthly	Thephorin	0	0	56,000	56,000	none	100%
16 M.L.	8 F	66	bi-weekly	Pyribenzamine	0	0	28,000	28,000	none	100%
17 H.C.	38 F	190	monthly	*Thephorin	0	0	56,000	56,000	none	100%
18 M.C.	10 M	88	bi-weekly	*Pyribenzamine	0	0	28,000	28,000	none	100%
19 D.V.	37 F	116	weekly	*Histadyl	0	0	56,000	56,000	none	100%
20 C.B.	34 M	195	bi-weekly	*Decapryn	0	0	29,000	29,000	1 with 1,250 PU dose	100%
21 P.L.	35 M	130	monthly	Decapryn	0	0	56,000	56,000	none	100%
22 E.L.	34 M	140	bi-weekly	Decapryn	0	0	56,000	56,000	none	100%
23 C.M.	13 F	103	weekly	*Histadyl	28,000	0	0	28,000	none	100%
24 R.B.	34 M	182	bi-weekly	Histadyl	0	0	56,000	56,000	none	100%
25 D.B.	30 F	120	weekly	*Thephorin	0	0	56,000	56,000	none	100%
26 M.P.	17 F	120	weekly	*Histadyl	28,000	0	0	28,000	none	100%
27 R.S.	26 M	130	weekly	*Pyribenzamine	28,000	0	56,000	84,000	none	Grass 95% Ragweed 50%
28 H.P.	29 M	210	weekly	*Neohetramine	0	0	28,375	28,375	1 with 500 PU dose	75%
29 M.H.	41 M	180	weekly	Neohetramine	0	0	56,000	56,000	none	50%
30 D.D.	15 M	137	weekly	*Benadryl	28,000	0	56,000	84,000	none	100%
31 K.C.	11 M	90	weekly	*Benadryl	0	0	28,000	28,000	none	100%
32 A.C.	39 F	150	weekly	*Tagathen	0	0	28,375	28,375	1 with 500 PU dose	100%

TABLE VII. RESULTS OF COMBINED HYPOSENSITIZATION-ANTIHISTAMINIC THERAPY IN FORTY-FIVE POLLEN SENSITIVE PATIENTS (Continued)

Case No.	Age and Sex	Lbs.	Injections Given	Antihistaminic Drug	Total Coseasonal Grass PU	Total Coseasonal Ragweed PU	Total Preseasonal Ragweed PU	Total PU Given	Constitutional Reaction	Clinical Result
33 R.D.	45 M	154	weekly	*Tagathen	0	0	56,000	56,000	none	100%
34 G.M.	23 F	167	weekly	*Tagathen	0	0	56,000	56,000	none	100%
35 J.M.	17 M	155	weekly	*Benadryl	0	0	56,000	56,000	none	100%
36 A.B.	25 F	102	weekly	*Pyribenzamine	19,250	0	0	19,250	1 with 5,000 PU dose	95%
37 L.M.	18 F	105	weekly	*Benadryl	0	0	56,000	56,000	none	100%
38 R.P.	35 F	121	weekly	*Thenylene	0	0	56,000	56,000	none	100%
39 J.R.	34 F	118	weekly	*Pyribenzamine	0	0	56,000	56,000	none	100%
40 M.D.	40 F	130	weekly	*Histadyl	0	0	56,000	56,000	none	100%
41 J.D.	56 M	230	semi-weekly	Benadryl	0	0	30,500	30,500	1 with 3,000 PU dose	75%
42 R.S.	37 M	145	weekly	Thephorin	0	28,000	0	28,000	none	100%
43 F.Y.	26 F	130	weekly	Thephorin	0	28,000	0	28,000	none	100%
44 E.W.	34 M	192	weekly	Thephorin	0	28,000	0	28,000	none	100%
45 D.W.	32 F	125	weekly	Thephorin	0	28,000	0	28,000	none	100%

*Patient exhibited side reactions to antihistaminic drug.

ate symptoms of several hours duration appearing intermittently throughout half the season and being more pronounced at the season's height.

Tolerance of Massive Pollen Doses.—The combined hyposensitization-antihistaminic technique safely allowed the administration of large doses of pollen antigen. The individual total amounts of ragweed pollen units injected preseasonally to nine patients, treated in 1947 without antihistaminic integration and in 1948 with antihistaminic preparations, were compared (Table VI). In 1947, these exquisitely sensitive patients tolerated small individual doses only and allowed a small dosage increase with each injection. Large increases produced systemic symptoms. Postseasonally, during 1947-1948, they were treated perennially and received their maximum dose at monthly intervals. However, preseasonally in 1948, when effectively protected with antihistaminic agents, they were able to tolerate from three to twenty-six times more pollen antigen without any untoward result.

Preseasonal Treatment.—Preseasonal ragweed therapy was administered to thirty-seven patients (Table VII). Six of these simultaneously received coseasonal grass injections also. Twenty-seven patients, over 100 pounds in weight, tolerated the scheduled doses of pollen antigen and each received, in eight injections, a preseasonal total of 56,000 pollen units of

ragweed. Four patients, under 100 pounds, completed their schedule and individually received a total of 28,000 pollen units in eight divided doses. The remaining six patients, Cases 1, 12, 20, 28, 32, and 41, all over 100 pounds, exhibited an exquisite sensitivity and developed mild constitutional symptoms with 10,000, 1,250, 1,250, 500, 500, and 3,000 pollen unit doses, respectively. As a result, the remainder of their schedule was decreased 50 per cent. Each received a total pollen dosage in excess of 28,000 pollen units.

All of the thirty-seven ragweed-sensitive patients had gratifying results. Thirty-two patients were adequately protected and had a 100 per cent result; three had 75 per cent; and two had 50 per cent. The latter were most enthusiastic because the improvement experienced represented the best result ever obtained.

Coseasonal Treatment.—There were fourteen patients, all over 100 pounds, who received coseasonal therapy; four ragweed and ten grass (Table VII). Six grass-sensitive patients concomitantly received preseasonal ragweed injections also. Thirteen patients completed their schedule and each received 28,000 pollen units in eight injections. The remaining patient, Case 36, developed a mild constitutional reaction with the 5,000 pollen unit dose and, because the remaining doses were reduced 50 per cent, received a total of 19,250 pollen units.

Twelve patients (eight grass and four ragweed) had a 100 per cent result. Two grass cases claimed excellent results (95 per cent). One patient, Case 27, had mild hay fever for one day lasting for a few hours while picnicking on the shores of a lake. The other patient, Case 36, sneezed occasionally during the early days of treatment.

SUMMARY AND CONCLUSIONS

Hyposensitization therapy and antihistaminic preparations have been integrated in such a manner as to present a new concept in the treatment of pollen allergy. The combined hyposensitization-antihistaminic technique enabled forty-five pollen-sensitive patients to tolerate safely massive doses of pollen antigen. They thereby attained a large total pollen dosage and the optimum single dose level within a relatively short time and with a substantial decrease in the number of required injections. The large pollen dosage conferred a tremendous degree of protection, heretofore not always obtainable, to all the patients during their specific season.

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SIGNIFICANCE OF MEDIASTINAL SHIFT IN ASTHMA

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THERE ARE various abnormalities which may affect the mobility of the mediastinum. In a healthy state, the mediastinum is not fixed, being mobile during the respiratory cycle. The mobile mediastinum responds by shifting laterally to equalize differences in intrathoracic pressure as a result of unequal aeration to a portion of a lung. Recognition of pendular shifts of the mediastinum are important in detecting complications of bronchial asthma.

ETIOLOGY OF MEDIASTINAL DISPLACEMENTS

In a healthy state, the descent of the diaphragm causes narrowing, and the ascent widening, of the mediastinum. Lateral recumbency causes a shift of the mediastinum and its contents to the dependent position. The diaphragm, on the same side, moves upward as a result of increased pressure exerted by the abdominal organs. The mediastinum widens when one assumes the prone position.

Unequal pressure in the two sides of the chest or traction brought about by disease often causes mediastinal displacements. Such traction may involve a localized portion of the septum or may result in a total dislocation of the mediastinum and its contents.

A permanent shift of the mediastinum and its contents is frequently seen in unilateral fibrosing pleuropulmonary diseases. The gradual contraction of the diseased organ and the compensatory emphysema of the contralateral lung cause the mediastinum to be displaced to the affected side. In the presence of an expanding tumor or an aneurysm in the upper aperture of the thorax, the trachea may be pushed to the contralateral side. Unilateral pleural effusion is a common cause of mediastinal displacement. The displacement may be prevented or minimized by homolateral bronchial obstruction or fixation by a previous mediastinitis and pleuritis. Displacement of the mediastinum may result from a high dome of the diaphragm from causes such as eventration of the diaphragm, subphrenic abscess and gas collections, especially in the splenic flexure of the colon and in the stomach.

Displacements of the mediastinum are often seen in bronchial spasm and in partial and complete bronchial occlusion with atelectasis, many cases of which are associated with the bronchial asthmatic state. One of the cardinal features of bronchial asthma is a narrowing of the diameter of the bronchi, usually seen in the smaller bronchi but in many instances

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These studies were made in the Radiology Department and associated clinics of St. Francis Hospital, Pittsburgh, Pa.

involving one or more of the larger bronchi. A partial or complete occlusion may occur. Therefore, in studying mediastinal shifts in the bronchial asthmatic patient, one must appreciate the many causes of bronchial obstruction:

Extrinsic.—Any extrabronchial disease which as a result of pressure on or invasion of the air passages might narrow or occlude the lumen of the tube.

Intrinsic.—Intrabronchial obstructions such as tenacious sputum, fibrinous casts, broncholiths, postoperative retention of secretions, foreign bodies, swelling of the mucosa, spasm, inflammatory stenosis, bronchogenic neoplasms, distortions of the lumen by some mechanical cause and congenital abnormalities should be considered.

It must be remembered that every wheezy chest is not necessarily a bronchial asthmatic chest and that any of the causes of mediastinal displacement might be the reason for the supposed asthmatic state.

PATHOLOGIC PHYSIOLOGY

The physiologic effects of tracheobronchial obstruction may be divided into their respiratory and their cardiovascular actions. An understanding of the manifestations of bronchial obstructions, especially as pertains to complications of bronchial asthma, is essential in determining the reason for a shifting mediastinum. Of major importance are the following: (1) the site of the obstruction, whether the lesion affects a single bronchus, several bronchi, or is diffuse; (2) the degree and character of the obstruction, whether partial or complete, simple or valvular, transient or permanent; (3) the time taken for the development of the obstruction; (4) the cause of the obstruction, whether within the lumen, in the submucosa or outside the bronchial wall; (5) the condition of the lung with respect to the presence of infection during the period of obstruction; and (6) the state of the pulmonary and systemic circulations.

The effects of bronchial obstruction are reflected not only in the affected bronchopulmonary segment but also in the uninvolved parts of both lungs, the circulatory system, the intrapleural pressure, and in practically all the contents of the thoracic cavity, depending on the factors previously mentioned.

In the presence of a slight degree of by-pass valve type obstruction, which does not interfere with the free inflow or outflow of air, no physiologic disturbances may be detectable. If it is of sufficient degree to interfere with free inflow and outflow of air, unequal intrapulmonary pressures may develop with a shifting mediastinum. Inasmuch as such obstructions are accentuated under stress, by periodic impaction of the lumen with secretion or by temporary swelling of the mucosa, the distal lung segment may undergo eventual changes.

In higher degrees of bronchial obstruction, in which a check-valve or ball-valve mechanism permits the inflow but prevents the outflow of air (Fig. 1), the bronchopulmonary segment distal to the site of obstruction becomes overinflated, since expiration is associated with reflex narrowing

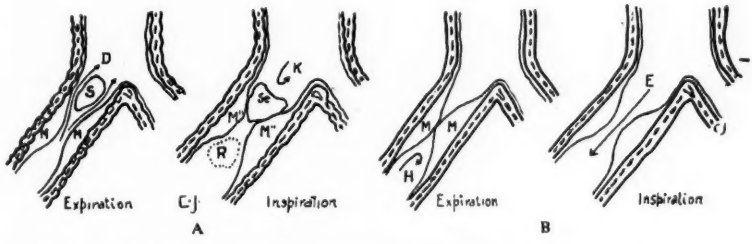

Fig. 1. (A) Mechanism of obstructive atelectasis produced by a small mass of secretion (S) acting like a check-valve in a pump. It rests in a valve seat of swollen bronchial mucosa at a bronchial orifice (M,M), but at each expiration it is lifted by the expiratory air current, allowing air to escape, as indicated by the darts (D). At the beginning of inspiration the suction pulls the mass (Se) down tightly in the valve seat, so that no air can enter (K). Repeated twenty-odd times per minute atelectasis results from pumping air out of the tributary area. A mass of secretion (R) below the inflammatory narrowing (M,M) would have the reverse effect of pumping air in, producing emphysema. Both these valvular mechanisms are seen every day in a busy bronchoscopic clinic. The resulting atelectasis or emphysema has been confirmed by physical signs and fluoroscopy.

(B) The expansile check-valve, which is the commonest form of valvular obstruction of the bronchi. The swollen mucosa (M,M) comes in contact at the start of the expiratory phase, preventing exit of air; but on inspiration, the enlargement of the bronchial diameter is sufficient to make a small opening for admission of air (E). Promptly at the beginning of the following expiratory phase the diminution of bronchial diameter promptly closes the narrowed lumen, trapping the air below the obstruction. Obstructive emphysema of the tributary area is the result. (Jackson and Jackson: Ear, Nose and Throat Diseases.)

of the bronchial lumen, causing the air to be trapped in the alveoli. This may become of sufficient degree to result in a shifting mediastinum. The condition gives rise to obstructive emphysema of varying degree and severity.

Complete obstruction, in which a stop-valve mechanism prevents the inflow as well as the outflow of air, causes atelectasis of the affected bronchopulmonary segment, the air trapped in the alveoli being absorbed by the capillaries within a few hours. Atelectasis may develop slowly or rapidly. There is a reduced lung volume in atelectasis and in any plugging or narrowing of a bronchus without atelectasis of sufficient degree to decrease inspiratory air in-take to a portion of lung. This serves to increase the normally negative intrapleural pressure. The mobile mediastinum shifts immediately to compensate for the loss of lung volume. The shift is toward the affected side on inspiration and, when severe enough, may remain displaced on full expiration. In the moderate to severe degrees of bronchial obstruction, the dome of the diaphragm is restricted in its downward motion and there is limitation of expansion of the hemithorax on the affected side. Additional compensation is affected by the distention of the uninvolved parts of both lungs. In obstructive emphysema, the lung volume increases in the tributary segment. When of sufficient degree, the medias-

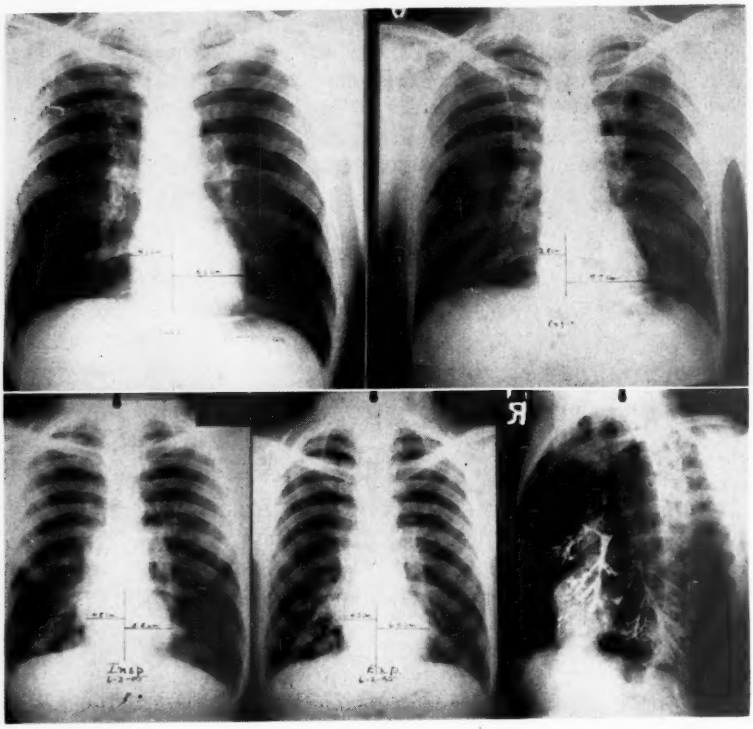

Fig. 2. *(above)* Films made on full inspiration and full expiration in an allergic bronchial asthmatic with a mixed type of infection demonstrate a definite inspiratory shift of the heart to the right. A more complete aeration is accomplished in the lower part of left lung on inspiration with a greater descent of the left dome of the diaphragm. On expiration there is a corresponding lack of egress of air from the lower part of right lung. These findings were due to mucus plugs in the lower right bronchial tree. All of the above findings disappeared soon after the plugs were removed.

Fig. 3. *(below)* The inspiratory and expiratory films of a chronic bronchial asthmatic with mixed type of infection demonstrate the inspiratory shift to the right more conclusively than the inspiratory film. Bronchogram (b) demonstrates stenotic narrowing of three branches of the right lower lobe and the right main stem bronchus and some cylindrical dilatation distally. All stenotic foci were subjected to repeated bronchoscopic dilatations with loss of mediastinal shift for some time, but bronchiectasis and abscess forced right middle and lower lobectomy.

tinum shifts toward the unaffected side in the expiratory phase and if severe enough may remain displaced on full inspiration. There is a limitation of upward motion of the dome of the diaphragm on the affected side and there is flattening of the dome and maintenance of an expanded hemithorax.

These compensatory physiologic changes are associated with phenomena which often result in permanent lung damage. In the bronchial asthmatic patient, the partial or complete bronchial occlusions due to spasm, edema, mucus plug or stenosis (Fig. 3) are the conditions which precede atelectasis, parenchymal inflammations, bronchiectasis, emphysema, pneumothorax and mediastinal emphysema.

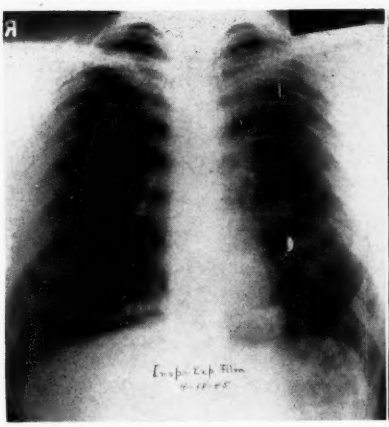

Fig. 4. This is a double exposure film, one exposure on full inspiration and one on full expiration, which shows considerable inspiratory shift of the myocardial shadow to the left in an allergic bronchial asthmatic with a mixed type of infection. This shift was due to mucopurulent plugs in left lower lobe bronchi and a small region of atelectasis in the lower part of left lung. The mediastinal shift was absent a few days after bronchoscopy, but the atelectasis was slower in clearing.

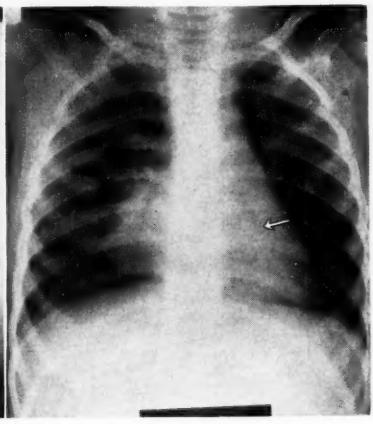

Fig. 5. Fluoroscopic observation and films made on inspiration and on expiration on a highly allergic bronchial asthmatic demonstrated an inspiratory shift of the heart to the left, which was found at bronchoscopy to be due to a mucus plug completely occluding a main branch of the lower left lobe bronchus. A sharp interruption of the column of air is faintly visible (arrow). Several bronchial stenotic foci were found in the right perihilar region of increased density with retained secretions distally.

ROENTGENOLOGIC OBSERVATIONS

The roentgenologic findings are of great value in detecting mediastinal shift. They are in keeping with the pathologic physiology as discussed. A conventional roentgenographic examination will not detect a shift unless it is marked. Fluoroscopy is particularly revealing since one can detect a minor pendular shift of the mediastinum by observing the heart and/or occasionally the aortic arch during the respiratory cycle. It may be recorded on two films, one made on full inspiration and the other on full expiration (Fig. 2), or on a double exposure film, one exposure on full inspiration and the other on full expiration (Fig. 4).

A pendular shift of the mediastinum may occur in an asthmatic bronchitis from any one of the several types of obstructive mechanisms. An inspiratory shift of the mediastinum may occur when there is an accumulation of secretion above a focus of associated swelling of the mucosa (Fig. 1, A), producing a check-valve obstruction on inspiration. The inspiratory shift to the affected side is all that may be seen (Fig. 2), but if this mechanism is prolonged and of sufficient degree, then atelectasis in one of the various forms depending on the size and number of bronchi or bronchioles so involved, may become apparent. When larger areas of atelectasis occur, a shift of the mediastinum is usually apparent in the conventional film of the chest, but it may be seen more readily on the fluoroscopic screen and/or with one or both types of inspiratory and expiratory roentgenographic examinations (Figs. 3 and 4). A plug in a fair-sized

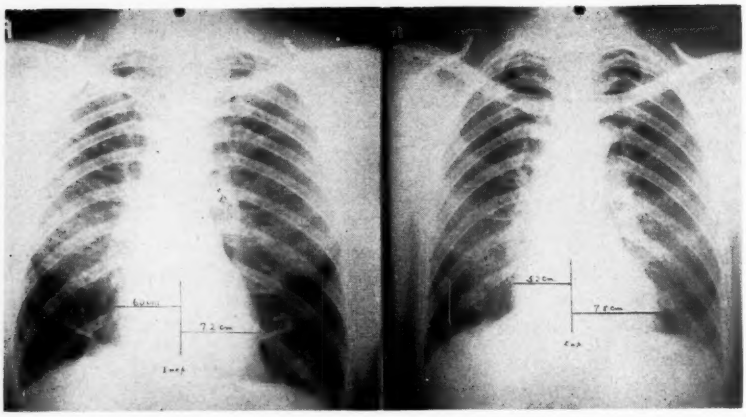

Fig. 6. Inspiratory and expiratory films of a chronic bronchial asthmatic with a mixed type of infection show emphysema at the bases and an inspiratory shift to the right. A chronic inflammatory constriction of the right lower lobe bronchus without any appreciable accumulation of secretion was dilated with known satisfactory state for two years.

bronchus without visible evidence of atelectasis distally may cause an inspiratory shift to that side even when there are several bronchostenoses with focal atelectasis in the opposite lung (Fig. 5). With the development of appreciable amounts of atelectasis, there appears a decreased range of motion of the diaphragm on the affected side with a higher dome on full inspiration. In the more pronounced atelectasis, a limitation of expansion of the hemithorax on the affected side becomes apparent.

There may be an accumulation of secretion below a focus of associated swelling of the mucosa (Fig. 1, R) producing a check-valve obstruction on expiration, or there may occur the expansile check-valve mechanism from a swollen mucosa coming in contact at the start of the expiratory phase, preventing exit of air; but on inspiration, the enlargement of the bronchial diameter is sufficient to make a small opening for admission of air (Fig. 1, B). With the development of emphysema, there develops an expiratory shift of the mediastinum to the unaffected side. When the emphysema is pronounced, it becomes apparent in the conventional film of the chest, but again the shift may be seen more readily on the fluoroscopic screen and/or with one or both types of inspiratory and expiratory roentgenographic examinations. With development of sufficient emphysema there appears a decreased range of motion and flattening of the diaphragm on the affected side with a lower dome on full expiration and maintenance of an expanded hemithorax.

Prickman and Moersch[4,5] have recently drawn attention to bronchostenosis as a common complication in either allergic or infectious asthma. The same pathologic physiology and the same roentgenologic findings pertain to bronchostenosis as are present in the bronchial asthmatic patient

with swollen membrane of a bronchus and a bolus of secretion above or below the point of stricture (Fig. 1, A, B). Bronchostenosis without secretion to produce a valve-like obstruction or without atelectasis may produce the inspiratory shift to the affected side because of a by-pass valve obstruction. Frequently in such instances nothing will be apparent on the conventional roentgenologic examination to suggest such a possibility (Fig. 6).

In a severe bronchial spasm with severe degree of emphysema where motion of the diaphragm is almost negligible, the ascent with widening and the descent with narrowing of the mediastinum practically disappear. The overdistended lungs keep the mediastinum in a narrowed and elongated state. With reversal of the greater portion of the emphysema, the normal mobility of the mediastinum returns.

Depending on the intensity, duration, degree and type of bronchial and/or bronchiolar obstruction, the lung changes may vary from that of acute bullous emphysema in a portion of one or all of one or both lungs to that of a massive collapse. There may be areas of obstructive emphysema interspersed with areas of atelectasis. Pathologic change may be of such degree and extent in both lungs that intrapulmonary pressure is equalized in each lung, so that there will be no mediastinal shift.

CLINICAL OBSERVATIONS

If any progress is to be made in reversing early stages of bronchial occlusion by bronchoscopic dilatations and bronchodilating drugs, it is believed that adequate roentgenologic study, which includes fluoroscopy and inspiratory and expiratory films, is absolutely essential. Detection of a mediastinal shift in the acute bronchial asthmatic state calls for adequate allergic management and repeated roentgenologic observations. If the mediastinal shift disappears, it may be assumed to have been due to a mucus plug. If it persists, bronchoscopic examination is indicated. Plugged bronchioles and occasionally a bronchostenosis may be found so that the bronchosocopist may be directed to it for bronchodilatations.

Symptomatically, there are features characteristic of bronchostenosis. There is often a severe persistent cough which fails to raise sputum and suddenly sputum may be profuse. The sputum is usually mucopurulent and often streaked with blood. Perhaps the most significant symptom of bronchostenosis is recurrent febrile episodes with or without preceding chills. This reaction may be very short or long in duration. Thus a history of frequent attacks of pneumonia is often obtained. The physical signs are very confusing and unreliable. In some instances they simulate the signs of a foreign body. There is usually a localized area of suppression of breath sounds.

In mediastinal shift with a history suggestive of bronchostenosis, immediate bronchoscopy and/or bronchography are indicated for diagnosis

and institution of proper treatment to aid in preventing or halting the progression of complications. An irreversible bronchostenosis is apparently an indication for thoracic surgery.

SUMMARY

The etiology and pathologic physiology of mediastinal displacements with special attention to the bronchial occlusion of the bronchial asthmatic patient are discussed. The roentgenologic observation of mediastinal shift by fluoroscopy and by inspiratory and expiratory films is stressed as essential in detecting, evaluating and treating the complications of bronchial asthma.

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AEROSOLS

(Continued from Page 769)

variables are in our present technique of antibiotic therapy than are desirable. The delivery of the nebulizer should be studied with a view to standardizing lung absorption and lung permeability. The inspiration time rather than the total time of administration was concluded to be of importance. An inspiration-time meter was devised and will be described in a following communication.

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SKIN SENSITIZATION TO BAL OINTMENT

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ONE OF THE great medical discoveries of World War II was the development of BAL (British Anti-Lewisite; 2, 3-Dimercaptopropanol) by Stockton and Thompson in R. A. Peters laboratory at Oxford, England.[8] It was developed by the British as a decontaminating agent and as an antidote for arsenical gas burns (Lewisite).[7] As an ointment it was used to prevent damage to the skin and eyes on exposure to Lewisite and vesicant gases. The above scientists proposed the theory that agents which "tie up" the SH (sulfhydryl) groups of tissues will interfere with cellular metabolism and tissue respiration.[7] BAL presumably exerts its beneficial effect by its selective affinity for certain metals, forming relatively stable, nontoxic and excretable compounds, thus preventing them from combining with the SH groups to produce toxic effects.[2]

Recent investigators have found BAL in a solution of peanut oil and benzyl benzoate to be a valuable and sometimes life saving drug in the treatment of systemic reactions, particularly from arsenic,[1] mercury[3,5] and gold.[6] This drug, however, is not without sensitizing potential and is capable of producing cutaneous allergic sensitization.[9] Many drugs of great therapeutic value are relatively harmless when used in the dosages recommended under controlled conditions for specific purposes, but may demonstrate marked sensitizing capacities when used indiscriminately and unwarrantedly.

The purpose of this report is to present five cases in which there was needless skin sensitization by such indiscriminate use. All of these patients had previous skin damage resulting from burns. Three had first degree burns and two second degree burns. The patients were wives of former servicemen who had been given the ointment with instructions as to its use and value in the event of Lewisite or arsenical vesicant gas burns. In each case BAL ointment was applied to the burned areas through an erroneous interpretation of its specific use.

SENSITIZATION OF DAMAGED SKIN TO BAL OINTMENT

During the years 1947 and 1948, five patients with papulo-urticarial lesions, surrounding erythema and edema came to the clinic with a tentative diagnosis of allergic dermatosis. The specific etiology was unknown and the type of sensitization was difficult to classify, as it differed from the eczematous contact type and the classical urticarial type. There was a lack of dissemination frequently seen in the eczematous type of sensitization with a complete absence of vesicles. In contrast to the typical urticarial

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type, scratch tests with BAL ointment in these cases revealed only mild to moderate erythema with no wheal formation.

The subjects suffered previous skin damage as a result of burns while cooking at home. A careful history revealed that the patients had applied an ointment to the burned areas from three to five times a day for six to thirteen days with a hope of hastening the healing process or preventing a progression of the skin damage. As stated previously the ointment was applied through a mistaken idea concerning its use. All patients were ambulatory and were requested to bring the ointment used to the clinic. It was later identified as 5 per cent BAL ointment.

Case 1.—A. J., a woman, aged twenty-two, was seen on June 4, 1947. She presented a healing first-degree burn on the left forearm with surrounding papulo-urticarial lesions accompanied by erythema and mild edema. The burned area, approximately 2 by 4 cm. was produced by spilling hot water on the arm when attempting to remove a pan of water from a stove six days previously. The patient stated that she applied an ointment (later proven to be 5 per cent BAL ointment) over the area three times a day until seen in our clinic. She was referred to the clinic because of the papulo-urticarial lesions with edema, pruritus, burning sensation and insomnia at night. The ointment was discontinued and the patient was given Benadryl, 50 mg. three times daily, phenobarbital, gr. 1½ at bed time, and ephedrine sulfate, gr. ⅜ three times daily. The lesions disappeared within five days; however, a brownish pigmentation remained at the periphery of the healed lesion for approximately four months.

Case 2.—O. B., a woman, aged thirty-one, was admitted to the clinic on July 3, 1947, with papulo-urticarial lesions on the terminal phalanx of the index and middle finger of the right hand with surrounding erythema and a burning sensation of two days' duration. Similar lesions with erythema and edema of three days' duration were observed on the left forearm. The patient gave a history of sustaining a first-degree burn by hot grease on the left forearm eight days before, and she had applied an ointment to the area with the fingers of the right hand. She stated further that she had experienced a similar burn on the left thigh by overturning a cup of hot water two weeks previously, to which she applied ointment from the same tube used in the present home treatment. The left thigh now presented small papulo-urticarial lesions with marked pigmentation at the periphery. There was intense pruritus in the thigh area which had been subjected to frequent scratching according to the patient. The lesions displayed marked improvement within three days after the discontinuance of the ointment and the use of ephedrine and Benadryl orally three times a day and phenobarbital at night.

Case 3.—A. C., a woman, aged twenty-two, was seen for the first time in the clinic on January 8, 1948. She presented confluent papulo-urticarial lesions (4 by 5 cm.) on the right thigh in the area of a healed first-degree burn resulting from an overturned pan of hot water ten days previously. There was also angioneurotic edema of the left eyelids and the left lateral aspect of the upper lip. The patient stated that she applied a "burn" ointment from a tube to the lesion on the right leg four to five times a day. She suffered from coryza during this period and frequently rubbed the left nostril and left eye with the hand which was used to apply the ointment. The patient admitted a continuance in the use of the ointment even though there was increased burning after each application following the fifth day. The

lesions cleared completely within six days after giving epinephrine subcutaneously, Benadryl orally and discontinuing the ointment.

Case 4.—D. G., a woman, aged twenty-six, was admitted to the clinic on February 12, 1948, at which time she presented a second-degree burn with an area of 3 by 6 cm. on the right forearm sustained by striking the arm against a hot iron. She applied an ointment (later determined to be 5 per cent BAL ointment) to the damaged area three to five times a day for nine days. The lesion did not heal but became progressively worse, with marked edema and intense pruritus. Scattered papulo-urticarial lesions formed at the periphery. The burned area was cleansed and a vaseline gauze dressing applied. Epinephrine was given subcutaneously, Benadryl and phenobarbital orally. The BAL ointment was discontinued and striking improvement was noted within three days. The lesions disappeared completely within twelve days.

Case 5.—A. C., a woman, aged thirty-four, was referred to the clinic on December 2, 1948, because of papulo-urticarial lesions surrounding a second-degree burn of the left wrist, with symptoms of burning and itching in and immediately surrounding the burned area. The inner aspect of the left thigh also presented an area, approximately 3 by 6 cm., with erythema, papules, mottling and edema. The injury to the wrist, 2 by 7 cm., was sustained by overturning a cup of hot coffee fourteen days before admission. The patient admitted that the damaged skin area of the left thigh was the site of injury by hot water two months previously. An ointment was applied three to four times daily to the wrist area for thirteen days and to the thigh area for six days before admission to the clinic because of marked pruritus without apparent benefit. However, the first-degree burn of the left thigh was treated in a similar manner for five successive days two months before without retardation of healing and a complete disappearance of symptoms. The ointment therapy (later identified as 5 per cent BAL ointment) was discontinued twenty-four hours before she was seen in the clinic because of nausea and a burning sensation in the mouth and around the eyes and nose. These symptoms evidently represent toxicity to the drug by rapid absorption as seen in cases of overdosage of the drug.[4]

DELIBERATE SENSITIZATION OF THE SKIN BY 5 PER CENT BAL OINTMENT

We were aware of the fact that the five patients discussed above were those with previous skin damage which possibly made sensitization less difficult. We wished to determine if 5 per cent BAL ointment would sensitize skin which was grossly normal if applied repeatedly. For this experiment we selected twelve patients who gave a negative history for allergic diseases. It was further determined that these patients had no previous exposure to BAL either in the form of an ointment, or a liquid. None of the patients showed evidence of skin damage resulting from burns, chemicals or physical trauma. Microscopically, the skin was obviously normal. Following a suggested procedure, as outlined by Sulzberger, Baer and Kanof, we attempted deliberate skin sensitization of the subjects.[10] Portions of the same BAL ointment used by the five patients with skin damaged by burns were applied by inunction in these twelve cases.

Procedure.—Each of twelve patients was instructed to rub gently a small amount (approximately 0.2 gram) of 5 per cent BAL ointment on the flexor surface of the left forearm two times a day. The approximate size

of the area selected for the repeated applications was 5 by 5 cm. We requested the patients to repeat the rubbing of a similar amount on the same area morning and night. They returned to the clinic at three-day intervals for observations and readings. If an eruption or marked erythema, which persisted for at least an hour appeared, they were instructed to discontinue the applications and report the same day for an inspection of the area and further recommendations. We regarded as positive sensitization only reactions of erythema which persisted with papulo-urticarial lesions.

Results.—Two cases showed evidence of sensitizations within twelve days.

The first case displayed marked persistent erythema on the afternoon of the fifth day, followed by confluent papulo-urticarial lesions on the sixth day. On the seventh day there was moderate edema extending approximately 4 cm. beyond the area of application.

The second sensitized case presented a moderate persistent erythema on the tenth day with numerous papulo-urticarial lesions on the twelveth day.

The remaining ten cases showed neither persistent erythema nor papulo-urticarial lesions after fifteen days of twice daily applications of the ointment. Patch tests with 5 per cent BAL ointment were made on the back of each patient before the beginning of the experiment. All were negative after forty-eight hours. These tests were repeated on the fifteenth day. The two subjects manifesting sensitivity to the ointment at the site of twice daily applications also presented positive patch tests on the fifteenth day. The morphological characteristics were similar to those resulting from inunction on the forearm. The patch test was negative in each of the ten cases with negative arm reactions.

Scratch tests on the twelve subjects revealed a mild erythema but no urticarial or wheal response. There was no apparent difference in the scratch tests response in the two sensitized subjects and the remaining ten non-sensitized subjects.

COMMENT

The type of sensitization in the five cases with previously damaged skin was somewhat difficult to detect because it differed from the accepted contact eczematous type and the classical urticarial type, yet possessing some features of both. None of these patients gave a history of previous sensitivity to drugs or previous allergic manifestations. Only on detailed questioning, the patient's description of the odor of the ointment used, and a subsequent check on the ointment brought to the clinic did we determine the allergenic agent in these cases.

There was evidence of a spread of sensitization in two of the five cases with burns as shown by erythema, edema and papulo-urticarial lesions at

distant points and postive patch tests on the back. The spread of sensitization was greater in those with previously damaged or burned skin areas than in those used in our control series with grossly normal skin. It is probable that the damaged tissue contained break down products consisting of large protein molecules which in combination with BAL molecules produced a drug-protein combination of relatively high sensitizing potential.

SUMMARY AND CONCLUSIONS

1. Five patients exhibiting first and second degree burns treated themselves with 5 per cent BAL ointment from six to thirteen days, with each presenting evidence of skin sensitization to the ointment. We have no way of knowing how many patients with similar skin damage treated themselves without evidence of skin sensitization.

2. All lesions of the sensitized skin were papulo-urticarial, with some erythema and occasional obvious edema, mottling of the skin, and increased pigmentation.

3. The lesions of sensitization dermatitis cleared on discontinuing the BAL ointment and using an antihistaminic and symptomatic therapy.

4. The lesions in the sensitized areas differed from the commonly accepted eczematous contact type and the standard urticarial type. Scratch tests were negative and patch tests displayed no vesicle formation.

5. The application of 5 per cent BAL ointment to grossly normal or undamaged skin of twelve subjects produced skin sensitization in two subjects. There was no history of allergic manifestations or previous exposure to BAL. The number of subjects sensitized is too small to establish a percentage incidence of sensitivity, but it does show that 5 per cent BAL ointment has a sensitizing capacity.

6. The relatively marked sensitizing potential of BAL ointment on damaged skin may be due to a combination of small BAL molecules with the proteins of injured tissue, forming a drug-protein combination of high antigenic quality.

7. Although BAL ointment proved to be a valuable drug during th recent war and has an important peacetime use for industrial arsenical poisoning, its power to sensitize must be kept in mind, especially if there is a history of its recent application to the skin and the lesions are papulo-urticarial in morphology with persistent erythema and edema.

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HUNGARIAN MEDICAL TRADE UNION ASSOCIATION OF PHYSICIANS, SECTION OF ALLERGISTS

Abstracts of Lectures Presented at Second Meeting, June 2, 1948

MYCOTIC INFECTION AND ALLERGY AGAINST FUNGI IN THE PATHOMECHANISM OF INFANTILE ECZEMA

E. LIEBNER, M.D.

THE general conception of food allergy in the pathogenesis of infantile exudative eczema, as based upon positive egg-white reaction, positive complement reaction and Praushitz-Kustner transference method, may be disputed as follows: (1) The skin-reaction is never eczematous. (2) It is never persistent, being positive in seborrheic dermatitis as well. (3) It is sometimes positive with varieties of eggs absent in the diet of mother and child. (4) Clinical symptoms rarely disappear or decrease with avoidance of the white of egg.

In 1938, Liebner succeeded in demonstrating fungi (varieties of oidia, trichophyton, epidermophyton, microsporon and molds) in twenty-one of thirty-seven cases of exudative eczema and seborrheic dermatitis; in 1947 in twenty-three of fifty-two cases of eczema; and in eighty-six of 109 cases of seborrheic dermatitis, corresponding with clinical characteristics known as microbiotic eczemata of adults; i.e., round, sharply outlined patches of centrifugal extension, scaling border, young efflorescences in the neighborhood and confluence into greater patches with serpiginous bordering with prevalently gluteal, perigenital and intertriginous localization of the first signs in areas predisposed for fungous infection. The appearance of lichenoid and eczematoid "ids" determines the polymorphism of symptoms and is to be explained by hypersensitivity. Patch-test with vaccines of oidia, pathogen fungi and molds gave positive eczematous reaction in eight of fourteen cases of exudative eczema; and in fourteen of thirty-one cases after several days it sometimes transformed into larger eczemata en plaque. The reaction was more prominent after scarification than on uninjured skin. No significant difference was found among the reaction of vaccines from oidia, pathogen fungi or mold. Sometimes positivity shows parallelism with appearance of "ids". Eosinophile cells may increase up to 15 to 32 per cent with lymphocytosis and leukopenia. Our investigations do not interfere with the question of pathogenesis in other cases devoid of demonstrable mycotic infection.

TUBERCULOUS ALLERGY AND BRONCHIAL ASTHMA

T. GLUCK

Bronchial asthma is a typical allergic disease. In most cases of asthmatic tuberculosis, allergy is demonstrable. Statistics of the author on the histories of asthmatics agree with the majority of research workers as follows:

(1) In approximately 15 per cent of the cases, hereditary tuberculosis

occurred. (2) 45 per cent of asthmatics had suffered from some mild form of tuberculosis (productive fibrous). The remaining 40 per cent of asthmatics derived their disease from various allergens, i.e., pollen, occupational disease, bacilli, toxins, et cetera. After complete recovery from mild tuberculosis, sooner or later, allergic conditions in the form of bronchial asthma may arise. Tuberculin had been introduced by Storm in 1926 in therapy of bronchial asthma. The majority of authors (Hajós, Kiss, Leibermeister) applied diluted tuberculin-solution (10^{-15}–10^{-5}). The author tried the same solution without success due to underdosage; therefore, he applied massive doses (0.01-0.03 gm.), after necessary precautions (blood analysis, history, x-ray, et cetera) and found that the association of fever raised the therapeutic effect of tuberculin. Sensitivity and asthmatic manifestations were reduced for months and even for years. No untoward effects of massive doses had been encountered. The author's experience, in accordance with that of others, seems to testify that, while allergic subjects resist serious tuberculous infection, the tuberculous organism does not incline to allergy.

DISCUSSION

L. Kiss: Kiss reports the effects of the tubercle bacillus as published earlier in special literature. In accordance with Gluck, he states that a great percentage of cases of bronchial asthma is based on tuberculous allergy. In opposition to Gluck's massive doses, he prefers caution, starting regular treatment with the limit-dosage of 1.10^{-15} gm., rising gradually in accordance with the method of Mantoux tests.

K. Hajos: Symptoms of past or present tuberculous infection were found in 21 per cent of asthmatics. Three and three-tenths per cent of cases of intrinsic asthma showed their first manifestation after tuberculous infection. Based on these findings, Gluck's view must be disputed, and tuberculin therapy used with caution. Tuberculin treatment cannot be mere fever-therapy, for which we have better-controlled methods. Tuberculin-treatment has its well-established indication and should be taken as specific desensitization, applying small doses. Fever-therapy in tuberculous patients may be dangerous.

PSYCHOSOMATIC ASPECTS OF BRONCHIAL ASTHMA

By K. HAJOS, M.D.

Psychosomatic relationships may be established by exact history-taking and detailed examination. Hence, in order to discover the psychic background, 1300 asthmatic patients were interrogated concerning the circumstances inducing the first asthmatic attacks. In 141 cases (11 per cent) the first attack followed nervous states, psychic excitement and depletion, while endocrine factors, with psychic and vegetative stimuli, caused the

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first attacks in sixty-two cases. In 723 cases, the first attacks followed influenza, severe colds and infectious diseases. It is striking that during deprivations of wartime, such as bombing, deportation, and ghetto-life, the majority of asthmatic patients felt well, which is due to the diminished functioning of the entire autonomic nervous system, and of the psyche.

For our understanding, emphasis of the great importance of the psychosomatic relationship, as correctly applied, and not dogmatic psychotherapy, seems to be advisable. Persuasion, psychagogy, suggestion attached to breathing-exercises, and even psychoanalysis are rarely recommended.

Physical immuno-biological effects and psychotherapy must always be associated. The new therapeutic view unites different methods and excludes both one-sided immuno-biological or psychiatric theories. Allergic diseases can only be treated with knowledge and correct estimation of both somatic and psychic factors.

METHYL THIOURACIL TREATMENT OF BRONCHIAL ASTHMA

By MARY-KATHARINE HAJOS, M.D.

After correct estimation of history-taking, psychic and physical influence, effect of drugs, and clinical picture, seven asthmatic patients with hyperthyroidism had been treated with Basethyrin Richter (4-methyl-thiouracil). Treatment lasted for several months, and gave satisfactory results in relieving both symptoms with the minimum of side-effects. No allergic reactions to the drug were noted. Generally, Basethyrin alone was sufficient in treatment, but in severe congestion, combined strophantine and theophylline therapy increased the effect of both.

Presented at the Scientific Meeting of the Apponyi Policlinic, March 5, 1948.

TESTING FOR IDENTITY AND PURITY OF POLLEN EXTRACTS

(Continued from Page 755)

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HUNGARIAN MEDICAL TRADE UNION, SECTION OF ALLERGISTS OF THE SECTION FOR CLINICAL MEDICINE

Abstracts of Lectures Presented Centennial Week, September 4-12, 1948

ALLERGIC RELATIONSHIPS OF DISEASES OF THE ALIMENTARY TRACT

PROF. DR. B. FORNET

ALLERGIC origin in gastritis may be proved by clinical symptoms appearing after allergen administration, hyperergic response of the mucosa, and presence of eosinophile cells. Generalized symptoms may appear in other organs. Desensitization and adrenaline give good results in treatment; cutaneous tests are positive.

Gastric ulcers of allergic origin are based on inherited disposition. Eosinophile cells and Charcot-Leyden's crystals in colica mucosa, recovery after ulcerative colitis from shock therapy, acute gastritis elicited by otherwise nontoxic agents, prove allergic origin. Occasional alimentary intolerance, allergic salvarsan and atophan toxicoses elicit allergic hepatitis. Anaphylactic experiments prove occurrence of allergic pancreatitis and pancreas necrosis. Pathologic permeability of the digestive mucosa and infectious enterocolitis may lead to allergic manifestations of other organs. Deficiency diseases may improve allergic complaints.

CONTRIBUTIONS TO CHEMICAL INCITEMENT THEORY IN HYPERSENSITIVENESS

PROF. DR. I. WENT

Biologically active substances creating anaphylactic symptoms may elicit anaphylactic phenomena after primary stimulation of various tissue-cells. Reduction of histamine sensitiveness by repeated histamine injections failed to increase histamine tolerance. Introduction of antihistamines proved to be inefficient. Biologically and pharmacologically active substances linked with protein molecules produce antisera, inhibiting the active group; thus increasing histamine tolerance by means of immunization. Treatment with histamine antigen (histamine-azobenzol-azoprotein, synthetized in 1942) protected experimental animals from toxic histamine doses and experimental anaphylaxis.

PHYSICAL ALLERGODERMATOSES

PROF. DR. E. RAJKA

Differential diagnosis of allergic skin manifestations elicited by physical agents and by chemical allergens are as follows:

Mechanical agents and light act externally alone; thermical agents have

internal effect as well. The physical agent reaches the stratum papillare of the intact skin; the reagin is linked to H-substances. Thermical agents may cause sharp-limited inflammation with additional distal effect via the lymphatic and blood streams. Passive transfer, in association with other allergic criteria, causes the allergo-physical process of fixed reagins.

ACQUIRED SENSITIZATION OF LIVER EXTRACTS

DR. G. GORTVAI

Allergic reactions of parenteral liver-therapy are rarely severe. Individual specific desensitization following history and intracutaneous tests, is advisable. In case of protracted desensitization, folic acid treatment should be encouraged. Passive transfer proves presence of reagins in hypersensitiveness. Since 1933, two cases out of forty-seven developed severe allergic reactions; seven of a milder degree.

RELATIONSHIPS OF ALLERGIC PAROXYSMS IN THE FEMALE SEX CYCLE

PROF. DR. K. HAJOS

Auto-endogenous hormone-sensitiveness may cause allergic symptoms associated with changes of hormone level and external hormone administration. Hetero-endogenous hormones may act as allergens.

Endocrine changes associated with the female sex cycle depend on allergic disposition and constitution, eliciting allergic paroxysms. Allergic symptoms are influenced by changes in endocrine functions through neurohormonal control, via autonomic nervous centers. This influence lies in establishment, disappearance or modification of paroxysms. In several cases of periodical hormone secretion, x-ray castration, estrogenic substances and progesterone improved symptoms. Sometimes, however, allergic paroxysms were inhibited by elimination of the central nervous factors dominating endocrine balance with chloral hydrate and barbiturates.

Allergic symptoms of pregnancy are associated with sensitization of the maternal organism by endogenous proteins (chorion, fetus). Towards the end of pregnancy, histaminase level rises in the blood serum. Treatment with pregnant blood-serum improved allergic manifestations.

HORMONE ALLERGY

DR. M. K. HAJOS

Tests for hormone sensitiveness with estrogenic and androgenic hormones (progesterone, pregnanediol, estrone, testosterone, androsterone) were performed in 107 cases of various allergic diseases, thus proving presence of hormone allergy with normal endocrine functions, and calling attention to its influence on diagnosis and course of treatment.

Forty-five cases showed positive reactions. Out of three cases of keratitis rosacea two were sensitive to progesterone, one to androsterone.

Importance of the tests lies in definition of relationships of changes of endocrine functions and hormone levels. Cases of estrogenic and progesterone sensitiveness were treated successfully with specific desensitization.

ALLERGIC DISEASE OF THE HEART

DR. B. LASZLO

A great number of infectious diseases are based on allergic sensitization. Susceptibility of myocardium and blood vessels to allergic reactions may elicit benign allergic myocarditis, such as late myocarditis in scarlet fever, with inflammation of the bundle branches. Streptococcal infection, erysipelas, and various foci may have the same effect. As regards treatment, the antigen has to be eliminated. Anti-allergic drugs and antihistamines may have a favorable influence on allergic myocarditis. Only cases of myocarditis with allergic criteria, positive skin tests and allergic symptoms are of allergic origin.

DIABETIC DISPENSERS IN PREVENTION OF COMPLICATIONS

DR. D. SIMOR

Statistical details of 1943-1945-1948 enumerate the complaints and complications of taking patients to the dispenser. Allergic response to insulin has been considered. The importance of treatment of diabetics lies in prophylaxis of developing complications. Association of asthma and diabetes, skin diseases and diabetes, as well as insulin desensitization, has been controlled with special care.

AN EVALUATION OF NEO-ANTERGAN IN DERMATOLOGY

(Continued from Page 782)

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

FOR THE SAKE OF UNIFORMITY

The manuscripts which pass over the editors' desks are gratifyingly uniform in their quality excepting for the occasionally very excellent and perhaps the rare not-up-to-standard paper. No two, however, are uniform in their use of abbreviations for units of measurement. Inches and centimeters, grains and grams often follow each other dizzily across the page to the despair of the editors, typesetters, proofreaders, and ultimate readers. Few authors have access to the Handbook of Chemistry and Physics. Since "order is Heaven's first law," it was deemed advisable to give this subject prominence by using the editorial page to list the abbreviations standardly used. Although the author is truly the final arbiter as to the units in which he wishes to describe his work, it would perhaps take little effort to bring papers on allergy into line with those in other fields of medicine and the physical and chemical sciences.

In measuring linearly, as for example, the diameter of a wheal, the standard abbreviation for millimeter and centimeter are respectively written as mm and cm with no period between or after either of the two letters. The abbreviation is exactly the same for both the singular and the plural terms. The square millimeter and centimeter are preferably written as mm^2 and cm^2 for measuring areas. The approximate equivalents for volumes are mm^3 and $cm.^3$ For units of mass each term for either the singular or the plural is abbreviated as follows: kilogram (kg) gram (gm) milligram (mg) and microgram (μg) with micromicrogram ($\mu\mu$g).

When measuring concentration the widest variety of terms has been permitted, although standard usage is concisely clear. One mole per liter is described as M/L with a millimole per liter as mM/L. One equivalent per liter should be abbreviated as q/L, and a milliequivalent per liter as mq/L; for one gram per liter gm/L and one milligram per liter the terms gm/L and mg/L are self-explanatory.

We are so accustomed to writing "the red cell count was 5,000,000" that we may perhaps hesitate at the scientific "$5.0 \times 10^6/mm^3$" for an erythrocyte count and "$5.50 \times 10^3/mm^3$" for a leukocyte count; usage has so sanctified the colloquialism. On the other hand, there is little or no excuse for what Ham* describes as that most confusing of terms "mg%." Its exact and only significance must be taken as milligrams of something in each

*Ham, T. H.: Laboratory data in clinical medicine. New England J. Med., 241:488, (Sept. 28) 1949.

hundred milligrams. The true abbreviation is therefore mg/100 ml or, when it applies, mg/L.

The author who uses the standard nomenclature will not only make his meaning more clear but will avoid the possibility of error due to the changes which must necessarily be made by those who must see his typescript through the steps of forming it into an acceptable printed page. He will also have the satisfaction of feeling that his readers will all know exactly what he is talking about.

CHRONIC ULCERATIVE COLITIS—AN ALLERGIC DISEASE

(Continued from Page 751)

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Progress in Allergy

MISCELLANEOUS ALLERGY—1949

Critical Review of the Literature

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In past years, the subject matter of this miscellaneous review has been divided into separate components and the discussion has followed this same trend. Of necessity, some mention has been made of important and interesting papers which have been cited and reviewed by other reviewers for ANNALS OF ALLERGY. In the following few pages an effort has been made to avoid such duplication and to offer only those words which rightly belong in this miscellaneous category and which, because of the subject, probably would be omitted from the other specified groupings. An apology is therefore extended to the authors whose works otherwise might have been included and to the reader who might herein expect to find material more closely identified with some other particular phase of allergic management.

That the practice of allergy is not all song and dance has been aptly proven by the report of Blanton and Sutphin.[9] The honesty of the authors is to be commended. All of us in the practice of this specialty depend to a great extent upon the reaction of tests being recorded as positive or negative. Yet these authors have demonstrated that negative skin tests cannot be overlooked even though their report is one of a fatality. Their patient was a fifty-seven-year-old asthmatic woman who had been previously examined and tested with positive reactions to various inhalants and pollen. Control of the asthmatic symptoms had been accomplished with oral medication. Preliminary scratch tests had failed to give positive reactions on this occasion, so intracutaneous testing was begun. The site of the testing was the back. Marked, generalized complaints of allergic shock were experienced by the patient after fifty-six tests had been injected. Death occurred within a very short time, and at the interval, all tests were thought to have been negative, although no real effort had been made to record the degree of reaction accurately. Autopsy findings showed both lungs to be markedly voluminous and in a state of constant inflation. Subpleural hemorrhages were found in association with submucous hemorrhages in the trachea and bronchii. Obstruction and occlusion of the bronchial tree were in evidence with edema of the mucous membrane which had infolded as a result of the intense spasm. Such unfortunate happenings are extremely unpleasant to experience, and each allergist should abide by the rule that conservatism in all respects is a valuable adjunct to each procedure. The danger of skin testing is further emphasized by the report of Rosen.[103] Symptoms of generalized reaction and collapse were noted in a female patient a few minutes after the introduction of 0.05 c.c. of a stock solution of streptomycin in intradermal manner. She had had a rash on the dorsum of her hands and on her fingers for several months. Though she had had no previous therapy with penicillin or streptomycin, she had been exposed to contact with each drug. Recovery from the reaction was obtained with emergency measures, and eventual passive transfer studies revealed only a moderate reaction to streptomycin. These unexplained violent responses are particularly upsetting, to say the least, to the physician in charge.

A fatality following the use of a protein digest (Amigen) has been the subject

of a report by Coppinger and Goldner.[23] The hypersensitivity reaction occurred immediately after the administration of not more than 4 c.c. of Amigen, with death following in a period of sixty minutes with all the classical signs of anaphylaxis present. Subsequent to abdominal surgery for a bleeding ulcer, this forty-four-year-old man was given Amigen solution, 5 per cent in 5 per cent glucose. Immediately the patient became apprehensive and complained of respiratory difficulty. The infusion was stopped with only 4 c.c. having entered the vein. The signs of reaction were progressive, with death occurring with the onset of pulmonary edema. Passive transfer tests were done with the patient's serum with the blood having been removed from the auricle at autopsy. These tests were positive. The authors suggest that all patients should be previously tested before the administration of protein digests parenterally. Equally unfortunate in its overall coverage is the editorial[31] concerning the present status of graduate education in allergy. A recent survey has shown that in the United States there are only seventeen institutions which offer adequate training in the specialty of allergy. Of these seventeen, only twelve of them are council approved. It is the suggestion of the committee that all institutions group their medical subspecialties for postgraduate training. The fact was also lamented that the better types of residents and postgraduate students were not being sufficiently exposed to the allergic diseases and their control, with the result that few of the so-called top personnel were entering the study of allergy as a method of practice.

Present-day aspects of allergy is the subject of an interesting discussion by Salmon.[104] He reviews the highlights in the development of present knowledge of allergy. Mention is made of the anaphylactic studies of Sewall in 1882 with various incidences involved in the progress of this specialty to the present standards. Though the care of the allergic patient will demand the efforts of the specialist in many instances, the man in general practice has the opportunity to relieve much suffering and to make the diagnosis in many instances. Bullen[15] emphasizes the importance of the history in making an allergic diagnosis. He presents a very sensible approach to the various methods of skin testing and offers an answer to his title question, namely, what should the general practitioner do about allergy? The author feels that the nonspecialist may undertake the necessary diagnostic studies and carry out the indicated therapy. This answer may be fraught with a pitfall or two. The general practitioner may also refer the patient for study and complete the treatment in his own office, which to this reviewer would seem to be the most sensible if the referring physician does not care to refer the problem in its entirety for investigation and treatment. Simon[113] has a very good discussion of the basic principles of the allergy investigation. He presents a paper concerning the specificity of the allergic reaction and mentions the usual management of the various allergic diseases—in addition, a few paragraphs suggesting an allergic basis for acute rheumatic fever, chronic arthritis and a few of the other presently unexplained conditions. Though skin testing is an important part of the allergy investigation, the history, examination and laboratory tests are necessary components of the complete program. Such is the advice of Spain[115] who feels that environmental correction for the allergic patient is a necessity. He has informed the ear, nose and throat practitioner in the details of recording an accurate and important history. Because these physicians will see the reactions, Spain also has discussed for them the signs, symptoms and therapy of drug reactions with advice concerning the serum sickness type of reaction. The concept that the "asthmatic state" is a constitutional factor is adequately supported by Rackemann in his annual review.[96] Such an attitude explains to a great degree the tendency in predisposed persons to develop one or more allergic diseases. McGee[76] feels that these allergic tendencies and trends may be recognized in the first year of life. Such recognition should lead the physician to careful addition of foods to the diet, with each food being

added singly, and no further additions until a three- to five-day waiting period for possible reaction has been accomplished. He finds it rarely necessary to skin test infants under the age of one year. In general, better results in therapy can be expected in children than in adults, and this is no doubt due to the better co-operation obtained from the adults as parents than as patients. With the thought that the pathologic condition in allergy is reversible, McGee is encouraged by his management of pediatric allergy problems. Ratner[99] has written that allergy may develop in children whether they are born into allergic families or to non-allergic families. All individuals are potentially capable of developing sensitivities. Fetal sensitization is possible in view of the ability of antigens or antibodies to be transmitted through the placenta. He recognizes the acquisition of hypersensitivity to be dependent upon constitutional or other factors peculiar to the individual. In addition, the amount of the antigen to which the patient is exposed is of importance. In Ratner's opinion, the quantitative factors are of greater concern than are the qualitative ones. Dietary regulation, environmental management, control of drug and serum therapy and reduction of recurrent pathogenic infections are important preventive measures to be accomplished. Skin testing in any age of patient is hardly worthwhile in drug allergy. Sherman[112] is of the opinion, and has the agreement of this reviewer, that an accurate history is diagnostic of drug sensitivity. Patch testing is occasionally of value, but the scratch and intracutaneous methods of testing are without value in an attempted diagnostic measure.

The usual estimate on the number of allergic patients in the general population has been recorded as 10 per cent. This figure can be accepted for most purposes, and is representative of the extent of clinical allergy. Prickman[93] states that the remaining 90 per cent may be sensitized under certain circumstances. This is particularly true with the administration of antitoxins, serums, penicillin or sulfonamides. Such reactions may be delayed or immediate in character. There is no sharp dividing line between the allergic and the nonallergic individuals. Prickman feels that the allergic reaction is a matter of threshhold, with this factor being lowest in the clinically allergic person. True allergic reactions are consistent and must meet the established criteria: symptoms must result from natural contact with a substance not provoking symptoms in the majority of individuals; the symptoms must disappear when such contact is avoided or prevented; and the original reaction must be reproduceable at will. He considers the allergic reaction to be a defensive process, with the symptoms being a resultant expression of contact with a noxious substance. "Failure to arrest allergic disease can be due to deficiencies in our understanding of the condition or to sins of omission or commission on the part of the physician who treats the patient." With such words, Cohen and Abram[19] present case histories illustrative of the reasons for lack of relief and improvement in the common allergic diseases. In their classification, mistaken or incomplete diagnosis is of the most importance and interest. Some patients considered as allergic are not truly in this status. Hence no improvement on allergic management can be expected, but often is anticipated. The symptoms may be initiated by allergy but continued by some other organic or emotional factor, the importance of which leads to continuation of symptoms in spite of supposedly adequate therapy. The failure to find the specific cause of the allergic symptoms is too frequently encountered. Inadequate therapy is one of the most important of Cohen's failure-clauses. If adequate co-operation of the patient cannot be obtained, then failure to improve will be the result. A word of caution should be extended to many physicians in this regard—the patient cannot be blamed for all failures of therapy! In many instances, the lack of proper explanation to the patient on the part of the attending allergist will result in the inability of the patient to adequately avoid the cause of the symptoms, even though such cause has been found, recognized and proven. Too much dependency on skin test findings alone will result in the failure

of the patient to show improvement. Similarly, the failure to appreciate the patient as an entity and to plan his management accordingly will meet with unpleasant therapeutic outcome.

The allergy factor in disease has been discussed by Cooke.[22] All manifestations resulting from antigen-sensitized cell reactions are included as allergic diseases. "Immediate" type of allergic response is shown by the reactions to air-borne allergens, as pollen, danders and dust. "Delayed" type of allergic response is shown by the tuberculin flare and is inflammatory in character. The antibodies, usually found in the globulins, are stimulated by contact of free cells with antigens. These antibodies may be beneficial, as in antitoxin, or their presence may be a liability as evidenced by allergic symptoms. Cooke states that there is still need for further study to prove or to disprove that sensitizing (allergic) and protective (immune) antibodies are the same. Histamine theory has failed to explain the delayed type of allergic response. He also has discussed the prevalence of allergy as a basis for the study of the pathogenesis of diseases of unknown cause—rheumatic fever, rheumatic arthritis, periarteritis nodosa, scleroderma, sarcoid, multiple sclerosis and the entire group of erythemas and purpuras. Cooke is a recognized advocate of his theory of the "earlier the removal of foci, the more satisfactory the results will be." Lesions affecting connective tissue have caught the attention of several authors. Duff[30] describes in detail the characteristics of connective tissue and the pathologic sequences seen in the various diseases—those mentioned above as of unknown origin. He postulates that a variety of factors, including hypersensitivy, may lead to the release of enzymes in connective tissue followed by destruction of collagenous and elastic fibers and to changes in the intracellular ground substances. A common etiology cannot be implied by similar morphological lesions. Criep[25] feels that hypersensitivity and collagen disease are often somewhat related. Serum sickness, which is a manifestation of allergy, is often characterized by collagen disturbance. More weight is added to this concept with the induction of periarteritis nodosa in both man and animals following the administration of sulfonamides or foreign sera. The clinical manifestations of rheumatic fever can be reproduced experimentally by sensitization. He adds a word of warning that it should not be assumed that the presence of collagen changes in man are necessarily and always caused by hypersensitivity. He echoes the views of the above authors that a common pathology does not necessarily bespeak a common etiology. In this same regard, Estrada de la Riva[35]advances a theory considering the disease, tropical eosinophilia, as an allergic reaction rather than as a nosological entity. He has shown that the allergic reaction is one of the organism to embryonic elements, extrinsic or intrinsic, with the hematopoietic system as shock tissue.

Occasionally periarteritis nodosa may be prolonged and not fatal. This is the standard of King[65] in his description of his patient with recognized and histologically proven lesions. A nonfatality over a period of more than two years is an oddity, to say the least. This patient, however, had asthma and arthritis of four years' duration with hospitalization necessary on several occasions. Eosinophilia varied from 8 to 54 per cent on several examinations, but at no time was there any evidence of renal involvement nor hypertension. Though the eosinophilia continued and she developed painful skin nodules from time to time, the course of the disease was followed over a period of many years. Gelfand and Aronoff[38] found that in their fourteen reported cases, 57 per cent had associated bronchial asthma. There was a noticeable rise in the incidence of periarteritis nodosa after the introduction of sulfonamides. In review of hospital records, they have recorded that there were relatively few cases in the years preceding the use of chemotherapy. In their fourteen cases, eosinophilia over 10 per cent was noted in 43 per cent of patients. The usual textbook picture of periartertis nodosa lays stress on the cardiac, renal and pulmonary aspects of the disease. Ralston and Kvole[97] could

find only one instance wherein hypertension was mentioned by the author. The kidney has been found to be involved most frequently with the vascular inflammatory lesions being the most characteristic pathological change. These authors have studied thirty cases with respect to the clinical evidence of renal damage; twenty-five of twenty-eight showed very early abnormal urinary findings, with the most common change being an early albuminuria; twenty of twenty-nine showed hypertension. The above prolonged instance of periarteritis nodosa gains in clinical rarity when it is reported that the average duration of illness in these thirty patients was found to be twelve months, with twenty of the thirty patients expiring within two to eight months after the onset of the symptoms. Again, it is emphasized that the site of the involvement is of utmost importance. It is concluded by Ralston and Kvole that there is no consistent correlation between the clinical evidence of renal damage and the specific pathological types. Well-distributed abdominal pain was the most frequent symptom noted in a study of thirty cases by Wold and Baggenstoss.[130] Five cases showed no lesions in the abdominal viscera although the complaint of abdominal pain was the most prominent symptom. Sweeney and Baggenstoss[120] found eight cases of lung involvement with arteriolar and parenchymal lesions. Fifty-two per cent of the cases studied had complaints of peripheral neuritis, as reported by Parker and Kernohan.[88] Eight cases had mononeuritis multiplex, but in seven instances the pattern was symmetrical multiple neuritis which clinically did not differ from infectious polyneuritis.

Harris and Laws[53] offer clinical and experimental proof that periarteritis nodosa has an allergic reaction as its base. If this disease is to be classified as an allergic disease, then several criteria must be met: perivascular infiltration with a fair percentage of eosinophiles and polymorphonuclear cells, edema of the vascular walls, fibrinoid necrosis and the variable factor of eosinophilia. The acute stage of the disease is manifested by an acute inflammatory infiltration reaching any of the three layers. Involvement of only one side of the vessel—segmental involvement—is characteristic of periarteritis nodosa. They feel that with better diagnostic work, the rate of recovery will increase. This reviewer again calls attention to the above remarks regarding the location of the lesions as an index to the rate of recovery or fatality. Gratifying clinical results in the therapy of rheumatoid arthritis have been reported by Rockwell.[102] In a series of fifteen adults, only two patients have failed to show improvement with the intravenous use of histamine, according to the principles of Prince, which produces a generalized flushing on administration. Some of the cases were given prolonged acting histamine in the form of ethyl histamine carbonate. Pain usually disappeared with therapy, and swelling was usually absent in three to six weeks. Blood sedimentation rates returned to normal within three to six months. He feels that the predominating pathological finding in rheumatoid arthritis is an impairment of the capillary circulation by a constricted capillary bed. In addition to the histamine therapy, bacterial sensitization and the removal of offending foods were adjunctives. Though he considers it unwise to attribute the entire syndrome of rheumatoid arthritis to food allergy, Zeller[132] presents four interesting problems in which dietary management was beneficial. Skin tests, both scratch and intradermal, were of relatively little value. The most effective and direct diagnostic aids were the food ingestion tests and the white blood cell response determinations. Concomitant allergic findings, a positive family history of allergy, positive skin test and passive transfer tests, blood eosinophilia, and x-ray studies are a few of the reasons for classifying some cases of arthritis as having an underlying allergic hypothesis. This is the opinion of Miller[84] in his presentation of three cases of allergic arthroses. A table is presented in offering a differentiation between allergic and nonallergic arthritis.

The subject of gout has been presented from the allergic standpoint by Hark-

avy.[51] He feels that heredity is an important factor in the production of the disease. Differentiation from other forms of arthritis can be served by the frequency of hyperuremia. He feels that the patient with gout may have an hereditary defect in his purine metabolism. There have been no previous reports of pollen or the synergistic effect of pollen and foods having any effect upon the initiation of the symptoms of gout. Harkavy reports three cases in detail in which it was possible to precipitate gout by allergic excitation. The ingestion of purine-and-fat containing foods was met without incident unless sensitizing substances were present. In one reported case, the symptoms were coincidental with the onset of the pollen season, and subsequently symptoms could be reproduced with pollen injections. This was true if wheat, one of the offending foods, were in the diet or if the pollen were in the air. Bacterial sensitization in two of the three cases suggests that the swelling in these instances was due to a vascual tissue reaction mediated by similar allergic mechanisms.

That desensitization is superfluous in insulin allergy is the contention of Hult and Jorpes.[58] They state that thoroughly purified insulin is tolerated by all diabetics. Even though some symptoms of sensitivity may be expressed, such conditions are lost after a continuation of the insulin for several weeks. Any difficulty can be obviated by using recrystallized insulin. They do feel that it is conceivable that a few extremely hypersensitive patients may become sensitive to the insulin protein. A "new concept in the treatment of allergy" presents a bit of discussion upon Ethylene Disulfonate. Ketcham[64] demonstrates that there are three paths for the chronic asthmatic or allergic patient to follow once he has been treated with this drug. These paths lead to good improvement, exacerbation of symptoms or no relief. The preparation of the patient, with avoidance of tobacco, alcohol, opiates, barbiturates and a few other materials is stated to be important. The reason for such avoidance seems to be that these products "have a tendency to inhibit dehydrogenase and the oxygen carrier system." The majority of reports concerning the use of this drug continue, as in the past, to state that Ethylene Disulfonate is without value in the treatment of the allergic patient. Phillips[90] found that 118 women between the ages of twelve and sixty years reacted negatively to a 1:5 dilution of Synapoidin. Twenty-five had positive reaction, with one patient showing shock symptoms from an intramuscular injection. The active allergen resides in the anterior pituitary hormone or its combination with chorionic gonadotropin. Antuitrin-S was used as a control test. Maximum dosage was 0.3 c.c. given intradermally twice monthly; thirty-five of forty-nine patients were completely relieved. Any dosage did not exceed the point of relief.

Thomas and his co-workers[123] have found that urticaria was the chief reaction to penicillin therapy in about 10,000 cases of syphilis. It occurred in about 2.5 per cent of the patients treated. The reactions were delayed in type, for the most part. This did not prevent the continuation or the resumption of therapy in the majority of treated patients. Another reaction, less frequently encountered, was an exacerbation of the secondary lesions of syphilis. This usually was noted at about the sixth to the tenth day following the institution of treatment. Lesions similar to an acute fungus infection, but with no demonstrable fungus found, were also noted as part of the penicillin reaction. Though the urticaria seemed to be recurrent over a period of several months, there was no noticeable permanent penicillin sensitivity demonstrated or reported. Treatment of pernicious anemia has brought to light specific instances of liver extract sensitivity. Malmros and Herner[80] desensitized two patients who had developed neurological lesions, and treatment with injectable liver extract could be continued. Fifteen other patients were adequately treated with folic acid and a stomach-liver preparation. It is recognized in general medicine that the use of folic acid is not to be accepted as adequate therapy in place of liver extract because of the failure of the former sub-

stance to affect neither the neurological lesions nor the progress of these symptoms.

During the past two years, this reviewer has had the opportunity of treating three cases of cold hypersensitivity. This may not seem unusual until it is learned that all three patients originated in the same part of the state and had their residences within three miles of each other in the country. They were not acquainted nor related. One of these three had symptoms to the degree of shock and collapse on an occasion when he was in the process of draining a small pond on his farm. Though his history of periodic swelling and urticaria upon exposure to cold had extended back into childhood several years preceding this severe attack, no accurate nor causative diagnosis had been made. Mullinger and Bogoch[85] report a severe case of cold hypersensitivity in a young woman who developed syncope while swimming in cold water. She was well controlled with Benadryl orally, in contrast to the personal experience in the three cases cited above. The benefit from this drug, however, was only transient, as the effect was dissipated within thirty-six hours. Histamine and cold desensitization were met with failure, which is in agreement with the reviewer's experience. These three patients have been comfortable while spending the cold Iowa winters in the South or Southwest. In this climatic regard, Schutzbank[108] has reported that 72 per cent of the patients coming to Arizona because of allergic disorders were the recipients of relief. Of 100 asthmatic patients, seventy-four received from 50 to 100 per cent relief. As a rule, the patient with an intrinsic bronchial asthma and a chronic sinusitis did not fare as markedly. In selected cases, the author felt that a change of climate should be recommended but that this advice should not be given to any and all allergic patients. The psychic aspect of the change may be more important than the climatic consideration. Arizona is dry and it has been stated that the dust-sensitive patient does not do as well there as in other regions. Stevenson[119] recommends the southern third of Arizona for the patient desiring abundant sunshine, warmth and little rainfall. Seasonal changes in that locality are seldom a noticeable source of distress to any patient. In contrast to the above climatic report, this author reveals that all forms of sinusitis, bronchitis and bronchial asthma are the receivers of health and happiness. He does state, however, that the infectious type (intrinsic?) of bronchial asthma will be relieved only after a period of several months or years in the Arizona atmosphere.

It has been often remarked, though far from accurately recorded, that only the so-called higher type of patient will find time to have allergic complaints. McAllister and Hecker[75] have reviewed a control group of 757 personnel and a test group of 1,875 psychiatric patients. Among the controls the survey was made during a ragweed season, and 21 per cent revealed major allergies, with 13 per cent having physical signs at the time of survey. The majority of the test group were definitely psychotic, with the incidence of allergy by history being 5.7 per cent, with physical signs of such hypersensitivity being demonstrable in 2.9 per cent. They wisely conclude, therefore, that the incidence of allergy is definitely less in the psychotic group.

Unrecognized allergic symptoms are often the causes for tonsil and adenoid removal. This has been brought forth by an article well written by Clein.[18] Following surgery, the mother usually returned with the child still having a good degree of nasal congestion and stuffiness—the original reason for the operation! All too often the diagnosis of allergic rhinitis is made postoperatively. In 27 per cent of Clein's reported instances, the patients who complained of lymphoid tissue regrowth were actually undiagnosed, untreated allergic children. A regrowth of lymphoid tissue was present in only 3 per cent of the investigated, treated group of children. It cannot be emphasized too strongly—and certainly anyone sufficiently interested in allergy to read this review does not need the advice—that the removal of the tonsils and adenoids does not relieve the symptoms of aller-

gic disease. The asthmatic patient presents the greatest problem as far as anesthesia is concerned because of the difficulty in breathing, increased pulmonary secretions, edema and congestion. Brenneman[13] feels that each of these patients should be well oxygenated. Ether abolished vagal reflexes and relaxes the bronchial musculature because of its sympathomimetic action. Rate and depth of respiration are increased with ether anesthesia by virtue of its stimulating effect on the respiratory mucosa. He feels that ether for these reasons, is the most useful agent. Nitrous oxide, ethylene, cyclopropane and others seem to be satisfactory, but Pentothal Sodium, because of its parasympathomimetic action, has a tendency to cause bronchial constriction. Seldom is there a reported instance of hypersensitivity to any of the inhalant anesthetic agents, although cyclopropane sensitivity is not uncommon. A great deal of the success of anesthesia in the allergic patient depends upon proper preparation of the patient, selection of the correct medication preoperatively and the choice of the anesthetic agent and technique. Substantiation of Coca's nonreaginic allergy is given impetus by Meyer.[83] He presents evidence to show that the pulse dietary method of diagnosis is a distinct weapon in the hands of the allergist. He feels, however, that it is too time-consuming for routine usage and has substituted intravenous histamine as the answer.

During the past two years, the attention of most allergists has been drawn to the public hearings held in Washington, D. C., in November, 1947, and January, 1948. These hearings were in regard to the possibility of allergy to cottonseed oil and the edible derivatives of this and other oil seeds. The testimony of the expert witnesses —G. T. Brown, R. S. McGrath, H. S. Bernton, J. H. Mitchell, K. D. Figley, M. H. Loveless—has been compiled in book form and published by the National Cottonseed Products Association, Inc. of Memphis, Tennessee.[122] If obtainable, the pleasant reading of the valuable material contained therein is an evening well worth the time of any allergist. Most of us have been in the habit of informing our cottonseed sensitive patients that they must, for fear of alarming reactions, avoid all products containing "vegetable oil." The average manufacturer does not differentiate between the edible oils and has found it convenient and practical to label any oil-containing product simply as such. This testimony should put an end to what Bowen[10] has described as an allergic ritual. Figley, one of the above testifying expert witnesses, has reviewed the material and presented it for general consumption. He has verified the fact (quoted by Bowen) that there is not a single reported authentic case of cottonseed oil sensitivity. In the one or two instances where such confirmation was in doubt, the suspected oil-sensitive patient was found to be nonreactive when the material was given and tested under controlled conditions and in masked form. It is accepted that the amount of protein in cottonseed oil is a negligible fraction. Figley has reviewed the above testimony in his presidential address.[36] Allergenic sensitivity to the water-soluble protein fractions of the various oil-producing seeds is common and severe. This should not be taken as an indication of oil sensitivity, however. The causative factor of any oil sensitivity must be some substance other than the water-soluble proteins of the producing seed. Additional evidence in published form is shown in the article by Bernton, Coulson and Stevens.[3] They describe two patients who were sensitive to the water-soluble protein of cottonseed. One of these (a physician) maintained that any contact with cotton would produce allergic symptoms and that the ingestion of cottonseed oil was followed by gastrointestinal symptoms. Masked feedings of several unlabeled (except for identification number) oils did not furnish adequate evidence of cottonseed oil sensitivity, in that the patient could not distinguish which oil was incriminated in his history. The authors feel that such controlled experiments fail to reveal any association between the water-soluble protein sensitivity and the clinical sensitivity to edible cottonseed oil.

In this same regard, there has been much discussion and debate concerning the sensitivity a patient may have for the parent source of other oils as contrasted to the specific oil sensitivity. Wolf[131] has inquired regarding the suspected sensitivity possessed by his patient for sesame oil. This was experienced and suspected upon injection rather than ingestion. Stenbuck[117] feels that his patient is responsive in an allergic manner (migraine) to the ingestion of corn and corn starch, but that no reaction could be elicited upon the use of corn syrup. Cazort[16] has carefully tested a suspected case of oil sensitivity, but more will be stated concerning this problem in a later paragraph. Detwiler[29] has disagreed with the established principles of Randolph and Rinkel in their method of determining food allergy. Though he feels that skin testing for foods is most unreliable, this author is of the opinion that an elimination routine is the one of choice. He places his patients upon an exclusively milk routine and adds foods as they seem to be indicated.

On August 3 and 4, 1949, there was another public hearing before the Federal Security Administrator. Though this was termed the "Bread Hearing," the decisive testimony concerned the likelihood of a patient being sensitive to corn and to the corn products or derivatives. Randolph testified that recognized sensitivity had been determined for corn starch as well as for the whole corn product. He was in favor of proper labeling of all food products in which any of the corn derivatives were contained.[98] Bernton,[4] in his testimony, felt that he did not see the 25 per cent corn-sensitive patients as had previously been described by Randolph. He was of the opinion that corn starch, corn syrup and dextrose did not act as allergens. He presented answers to a questionnaire that would tend to show that such a large percentage of corn-sensitive patients was not usually seen in the average allergy practice. Cazort[17] testified concerning his patient who was known to be sensitive to whole corn. Under controlled conditions, this patient had been given one ounce of corn syrup in Coca-Cola and no symptoms could be elicited. Later, one-half ounce of corn oil was given without producing symptoms. The same patient held a half a teaspoonful of raw corn starch inside his lip with no immediate nor delayed reaction. Cazort felt that this confirmed his opinion that the antigen of corn oil, corn starch or corn syrup was "negligible clinically." This patient had a marked, immediate, wheal-type reaction on scratch test with corn meal. A repetition of the test with contact to the lip with corn meal was followed by immediate tingling of the patient's tongue, and with redness and swelling in the area of the tonsillar pillars. Similar feeding tests with corn meal in this patient had been associated with almost alarming symptoms upon ingestion. Halpin[46] added to the testimony with a description of a patient clinically sensitive to whole corn. This patient had had immediate asthma, urticaria and almost collapse upon the ingestion of corn on more than one occasion. Allergy investigation had revealed, in part, a marked immediate wheal-type reaction to corn extract and corn meal on scratch test. Masked feedings of products unknown to either the patient or the physician were not associated with any symptoms, either objective or subjective. It was later determined, just prior to the presentation of the testimony, that the feedings had been, in order, a control of arrowroot, tapioca and corn starch pudding. The sweetening agent was determined to have been sucrose. The puddings all had similar appearance, consistency and taste. The conclusion was therefore drawn that this known corn-sensitive patient was not reactive to corn starch and therefore the antigen in corn starch was negligible clinically. Rawlings[100] had performed controlled feeding tests in the same manner with the same results. He described the patients and the ingestion of masked puddings. He felt that his patient was allergic to fresh corn but not sensitive clinically to corn products nor derivatives.

Of twelve patients who received a full course of intramuscular penicillin therapy, seven were apparently benefited. The complaints were those of chronic asthma. It was necessary to discontinue treatment in three patients because of reactions.

Sterling, Fishman and Sharpes[118] feel that the improvement is due to the specific antibiotic effect of the drug, which thus reduced the frequency of bacterial infectious processes and exposures. In the past few years, much writing has been relative to the use of radon or radium to the nasopharynx of asthmatic children. In answer to a query offered by Piness[91] it was the feeling of Barnet[2] that such procedure was well worth while. Hansel[47] stated that the use of radium applicator would be entirely nonspecific in nasal allergy. Its use should be advised only in those instances where all other forms of accepted therapy had been judged a complete failure after adequate trial. Jones[62] had no unpleasant experiences with radon and radium in the treatment of lymphoid hypertrophy of the nasopharynx. He describes the currently accepted method of treatment as using 50 mg. radium filtered with 0.1 mm. monel metal. The applicator is applied in each side of the nasopharynx so that the radium is close to the orifice of the eustachian canal. The applicator is left *in situ* for twelve minutes on each side. Treatments are repeated at stated times and intervals depending upon the result. The patients of Cohen and Fisher[20] were divided into groups depending upon the amount of adenoid tissue, the degree of hyperplastic sinusitis, and an elevated sedimentation rate. They did not consider this form of therapy as a panacea for all forms of asthma in children. They did find it to be a good auxillary, however. Expected improvement was noted about seventeen weeks after the application of a radium applicator for six and one-half minutes in a dosage of 100 mg. The higher the sedimentation rate, the better seemed to be the result. More relief was obtained in the group possessing a small amount of adenoid tissue as compared to those with a great deal of the tissue present. Patients with normal sinuses seemed to fare better than those with hyperplastic sinusitis.

The importance of allergy in the average ear, nose and throat practice has been emphasized by Hansel.[48] He lists the frequency with which the nose and paranasal sinuses are involved, and in order they seem to be (1) allergy, (2) allergy with secondary infection, and (3) suppuration. A good discussion is presented of the symptomatology, bacterial flora and pathology. The examination of the cytological specimens is of great importance, and instructions are given, with which most allergists are, or should be, familiar. As part of the same symposium, Black[7] discusses the history and its importance. Determination of dosage, with indicated titration and low-dosage requirements are a part of this presentation. Ashley[1] adds that the success of allergy management depends upon an accurate diagnosis. He advocates extremely low dosages in therapy. Of all factors, he feels that the inhalants are of the utmost importance with the house dust substance being foremost. Although the allergen, house dust, is recognized as being of greatest importance, little has been determined quantitatively of the nature of the active constituent. An editorial[32] calls attention to work that has been done in this regard. The paragraphs quote from published works of Rimington, Stilwell and Maunsell who have described a purified antigen containing 25 per cent hexose and 2.5 per cent nitrogen. Before and after mild hydrolysis, the antigen shows two main components electrophoretically: one mobile and colored and the other immobile and colorless. They are somewhat similar in composition and antigenicity. Harrell[52] continues the recognition studies of allergy by the otorhinolaryngologist. He emphasizes the importance of avoiding as much intranasal medication as possible. If used at all, this should be nonirritating, isotonic and with a slightly acid pH. Because they are mostly alkaline, sulfonamides should be limited in their use in the nose. Surgical procedures should be kept at a bare minimum, with submucous resection and antral windows deferred until an adequate allergy study has been made and followed. The soft tissue of the turbinate is the primary shock organ in allergy of the upper respiratory tract. This is the statement of Schenck.[107] The pathologic picture is a thickening and hyperplasia of the epithelium, edema of the basement

membrane and edema with eosinophilic infiltration of the stroma. A specific allergen is capable of precipitating all these as secondary phenomena to vascular changes. The efficiency to combat infection is definitely lowered in this type of allergic tissue. A radical ethmoid sinus attack is indicated only in failure of allergy program. Turnbull[126] presents twenty-five cases illustrative of various manifestations of allergy. There is a slight feeling that all of these patients are not truly allergic, as shown by his description of Case 16: a thirty-five-year-old man who consulted the author with no presenting complaints but did admit upon questioning to having had "mucus in his throat." This disappeared in two weeks with adequate dietary management.

The high incidence of allergy in bronchiectasis and chronic bronchitis emphasizes the importance of proper allergic therapy in some infectious processes of the lungs. Davison[27] found that 76 per cent of the patients with bronchiectasis were allergic. All had undergone bronchoscopic examinations. Green[44] has reported on the use of aerosol penicillin in allergic patients with respiratory infections, with the coverage being for the year October, 1946, through October, 1947. Over 200 aerosol treatments were given to seventy-nine allergic patients. All symptoms were referrable to the respiratory tract. The average patient was given 10,000 units of penicillin by aerosol with epinephrine 1:1,000 or some other similar solution. The author feels that this has been an adjunct of use to his forty-two cases of asthma, eight cases of seasonal hay fever (why the penicillin?) and twenty-nine patients with allergic rhinitis. Maietta[79] has used epinephrine 1:1,000 as an aerosol with good results in bronchial asthma. Its action here is that of a topical vasoconstrictor. The relief of mucosal edema dislodges the inspissated mucus. Bronchodilation is a secondary effect of the medication used in this manner. Usually 0.5 to 1 c.c. is given with oxygen at a rate of 6 liters per minute. He has reported on this medication as used in seventy-three patients with excellent results. Markan[82] and his co-workers have reported on the use of intravenous oxygen in bronchial asthma. The rate of oxygen intravenously is 600 c.c. per hour using the Ziegler Technique and apparatus. It is permitted to flow from two to seventeen hours. Vital capacity was increased in all cases from 300 c.c. (30 per cent) to 1,300 c.c. (87 per cent). The increased vital capacity remained for as long as eight months in some cases, but there was a recurrence of symptoms in all instances within six months. Additional aids in the relief of bronchial asthma are found. Reiser and Ferris[101] have used the Drinker respiratory in three cases of bronchial asthma. Two of these died as a result of cerebral anoxia (??) because the procedure was delayed in action. The application of positive pressure to the chest wall and abdomen is thought to be a good adjunctive to the routine treatment of severe bronchial asthma.

Levin[72] calls attention to the importance of soil molds in respiratory allergy. She states that in Chicago the most important clinical mold is Alternaria. By the slide method, only Alternaria, Hormodendrum, Helminthosporium, rusts and smuts can be identified. Hormodendrum is the second most frequently found mold on the slide. Alternaria is seasonal as well as perennial and has an affinity for wheat and grains. In their office (Unger's) a mold mixture is used for therapy. This is made up of Alternaria 50 per cent, Hormodendrum 30 per cent and the others 20 per cent. Good results are obtained. Prince and his co-workers[94] have given the green light to their extract, labeled Alternaria No. 33. They have interesting tables to show the superiority of this extraction in Alternaria-sensitive patients and in control studies as well. This reviewer can second the statements, for this extract has been found most reliable in the examination of many Alternaria-sensitive patients, and in comparative studies with other commercial extracts. They have demonstrated that a precipitation with nine volumes of acetone gives an extract of higher potency than any other previously studied material. That air-borne molds may be either a primary or a contributing cause of respiratory allergy is the contention of

Eisenstadt.[34] The predominant molds in the Minneapolis area are essentially those as given above for the Chicago zone. Penicillium and Aspergillus are perennial contaminants with the rest being primarily seasonal. Multiple mold sensitivity has been found to be the rule, rather than the exception. Reactions were found to be clinically significant in 29 per cent of all the patients tested (380) and were of direct, first-hand importance in 11 per cent. Bieberdorf and Argabrite[5] feel that better mold extracts can be prepared by the use of protein-free media. This eliminated the additional number of washings, and yet such extracts were more potent though they contained the same nitrogen value as their predecessors grown on protein media.

Inhalant allergy as a cause of dermatitis has been propounded by Tuft.[124] The outstanding offenders in his report have been dust, ragweed and wool. The initial symptom of such inhalant dermatitis is intense itching. Once the lesions are present, other factors such as emotional influences and upsets may play a decided role in the aggravation of symptoms, signs and duration or extent of the appearance. Several illustrative cases are cited. In some geographical areas, an inhalant mold sensitivity is also of primary consideration. Though it is an important, neglected factor, inhalant allergy is not the sole cause of atopic dermatitis in older children and adults. The author emphasizes the point that proper local therapy by a *good dermatologist* is very important for good results. A case of hereditary angioedema has been reported by Sheldon, Schreiber and Lovell. These authors[110] present a case report from a family wherein edema affected three and possibly three additional members in two generations. Histamine and intravenous Benadryl may have been beneficial in some respects but they did not prove adequate in protecting the patient from fatality. Death was due to uncontrolled edema.

There has been considerable writing and literature concerning the use of undecylinic acid in the therapy of psoriasis. Perlman[89] administered the drug orally to seventeen patients with definite psoriasis and to eight patients with neurodermatitis. Excellent results were revealed. Gradually increasing dosages of the drug were given until a total of 7.5 grams were taken daily. All cases showed improvement with pruritic relief, and no harmful effects were noted even after prolonged therapy. Sheldon[111] used undecylinic acid without benefit in three patients with atopic dermatitis. The first patient received peak dosages of 6 grams three times daily for six weeks with no influence upon the severity, progression or duration of the lesions. The dermatitis was typically an atopic eczema of long standing. The second patient had a life-long history of eczema and his peak dosage was 4.8 grams three times daily. Therapy was continued for eight and one-half weeks. The same dosage was given to the third patient, a young lady with eczema. Treatment was continued for five weeks before failure was recognized and admitted. Ointments containing mercury often will lead to a prolongation of the lesions of plant dermatitis. Underwood and Gaul[128] decided upon this as a result of 152 exacerbations of dermatitis in 202 patients. These treatment reactions occurred most frequently at the site of the original lesions. Edema, vesiculation, bullae, hemorrhage and pustulation were the usual signs of such reaction from therapy. Leider and Baer conclude from their experiments that it is impossible to transfer passively allergic eczematous hypersensitivity.[69] Dermatitis was produced in six sensitive patients by patch testing for forty-eight hours. When the produced reactions had reached the stage of involution, cantharides blisters were raised on the healed sites. The injection of this blister fluid into the skin of normal persons failed to react in the expected manner when patch tests were applied to these prepared areas. Not all contact lesions are of the typical type. Urticarial lesions produced by contact were somewhat of a rarity. These were determined by Cole, Marmelzat, and Walker.[21] Their patient had suffered with giant urticaria of several weeks' duration. Efforts at the usual measures of relief were to no avail, until it was revealed that one flare-up during hospitalization

was associated with the use of an estrogenic cream. Past exacerbations were also connected with the use of this agent. Aminophylline has been used primarily in the therapy and relief of the allergic symptoms of bronchial asthma. Turner[127] treated thirty-five patients in the emergency clinic at Grady Hospital, Atlanta, Georgia, for urticaria with this drug by the intravenous route. One patient, in particular, showed dramatic improvement in the lesions and complaints that were thought to have been due to a spider bite. Complete relief was experienced by fifteen of the thirty-five patients and partial relief in eleven. The effect of the aminophylline was comparable to that of epinephrine.

Hauntz and Grinnell[55] have carried out studies to determine the incidence and severity of reaction to the various forms of prolonged-action penicillin. One hundred and forty-two patients were used in this experiment; 100 of them had penicillin in beeswax and oil; sixty-three received procaine penicillin G in peanut oil, and seventeen had procaine penicillin G in aqueous suspension. Some patients were given more than one type of injection. Eleven patients developed sensitivity reactions among the 100 that had been given the beeswax and oil preparation. Only one reaction occurred in the procaine penicillin G in peanut oil group while no reactions were found in the aqueous suspension classification. They recommend the abandonment of the beeswax and oil preparation of the drugs, because this substance seemed to be the sensitizing agent. Samitz and Horvath,[105] on the other hand, have presented two patients in whom the reactions seemed to be due to the sensitivity to the penicillin itself. In such instances, testing the patient is accompanied by some danger of exacerbation and continuation of the lesions under therapy. Intracutaneous testing for drug sensitivity is unreliable in the opinion of Hansen-Pruss.[50] In the past two years, he has studied a group of twenty-six patients suspected of being sensitive to drugs. Their particular interest was in the group of medication of analgesic or antipyretic effects. Intracutaneous tests were done with solutions of the suspected drug, and to serum obtained from patients supposedly saturated with the drug. Contact tests were done on six patients and passive transfer studies were carried out on an additional five cases. Further work included testing "blister fluid" and actual readministration of the agent. Test and control patients responded in the same manner to the intracutaneous test, and hence this method proved unreliable. Passive transfer studies showed that aspirin is a strongly allergenic substance but they were not dependable for definite conclusions of specific sensitivity.

Until recently it has been a problem with this reviewer to adequately correct infantile eczema with substitution of a soybean preparation for milk in the diet of a milk-sensitive patient. The difficulty usually arose with a call from the mother seeking information as to methods to correct a moderate to severe diarrhea in the infant whose skin lesions were clearing with such substitution. Glaser[40] answered my questions with the addition of one or two teaspoons of Kaopectate to each bottle of soybean milk. He went further to offer a very adequate substitute for the infant who reacted to both milk and soybean mixture. Quoting from a previously published article[41] he listed the ingredients of a strained meat formula which is of sufficient importance to bear repetition in this review. Direct copy of this formula is shown on the opposite page.

The atopic and contact types of infantile eczema are based on allergy, but the conditions named numular eczema, seborrheic dermatitis and fungus infections—all of which are often classified as eczema—are not upon an atopic basis. Hill[56] does not believe that all positive cutaneous reactions are of clinical significance. To properly determine whether a food should be incriminated as a cause of the eczema, it must be eliminated from the diet, but care should and must be taken to insure an adequate, nutritious intake of food. Milk should not be removed from the diet unless a positive skin test reaction to milk has been elicited. Soybean substitution

is more successful than the use of goat's milk. Some forms of infantile eczema are due to contact sensitization rather than ingestion. Antihistaminics and unsaturated fatty acids have been generally disappointing in their relief of the lesions. Local therapy is incomplete without the additional aid of proper bandages for protection and prevention of further irritation of the lesions through scratching.

STRAINED MEAT FORMULA

Strained lamb (or other strained meat)	1⅛ cups
Oil—Sesame, olive or Mazola	2½ teaspoons
Sugar	2⅔ teaspoons
Starch—potato, tapioca, rice	2⅓ teaspoons
Calcium carbonate (get 4 oz.)	1 teaspoon
Ordinary table salt	½ teaspoon
Water	5 cups

Heat water in the top of a double boiler until the water in the outer boiler starts boiling. Add the sugar, salt and calcium carbonate. Mix the starch to a paste in ⅓ cup of cold water and stir into the water in the top of the double boiler. Cook the mixture for 45 minutes in the top of the double boiler, stirring occasionally to prevent lumping. If necessary, add water to allow for evaporation. Then add the strained meat and oil and mix thoroughly. Make up to 1 quart with boiled water. Bottle and use as formula.

Simon[114] has described fourteen cases in which human dander has been classified as a distinct cause of the eczema. He believes that this is the most important known allergenic excitant of the disease but states that it is likely that this is not the most important existing allergenic excitant. By testing, he has determined that the lesions of certain cases of atopic eczema contained an eczematogenous agent which was not a primary irritant but was most likely an allergen of undetermined chemical nature and biologic origin. Leider and Furman[70] describe causative factors of dermatitis ranging from occupational substances to "falsies" (non-occupational?).

So much has been written in the past few years concerning the antihistamine drugs that no attempt could possibly be made to review the literature in this space. The material is worthy of a separate review in itself. Besides, the journals are filled with comparative experiments lauding one and mentioning others to such a degree that a reviewer would be in a constant whirl trying to maintain some sort of equilibrium and balance. Ocular allergy has responded well to the use of Antistine eye drops. Hurwitz[59] has used the drug locally in fifty reported cases; 84 per cent of these patients were the recipients of benefit. Most relief was experienced by the ragweed sensitive patients. The drug seems to have a cumulative effect. Two of his patients were adequately relieved of their associated photophobia. The immediate effect of Antistine is contraction of the superficial vessels and a blanching of the conjunctiva. Vascular constriction is prolonged and not followed by secondary vasodilatation as is noted with epinephrine. There is also a slight anesthetic effect with Antistine. Loveless[74] has listed her preference for the antihistamine drugs in the order of: Pyribenzamine, Trimeton, Neo-Antergan, Decapryn, Thephorin and Antistine. These drugs were compared clinically and their efficiency was about in the order as listed. Of the above medications, Thephorin and Antistine were said to be associated with less side effects, while Decapryn seemed to disturb more patients than the other drugs. Her work was done with 113 patients suffering with ragweed hay fever. Harris[54] found essentially no difference nor preference in the five drugs studied in various allergic cases. Hydryllin semed to be more effective in bronchial asthma than did the other antihistaminic preparations used by him. Pyrrollazote was thought by Zolov[133] to be less effective than some of the other more commonly used medications of this group of drugs. That the use of antihistaminic medication in allergic conditions is not always beneficial is stated in a

few paragraphs by Braden.[12] He has described the occurrence of urticaria due to the use of Benadryl and Pyribenzamine. Aggravation and actual production of urticarial lesions were witnessed in his patient under treatment for ragweed seasonal hay fever. Schilling[109] had a similar experience with the use of elixir Benadryl given for the relief of severe dysmenorrhea. Urticaria was produced by the medication, and cleared with the withdrawal of the drug. Reproduction of the lesions was not attempted. In answer to a questionnaire, concerning the production of eczema by the use of an antihistaminic drug, eight answers[95] failed to agree with the cited instance. None of these eight had noted the presence or association of eczematous lesions with the use of Benadryl or similar preparations. The same reference reveals a listing of the preferential medication used by several men over the country. Benadryl seemed to be the drug of choice where sedation was desired, whereas Hydryllin seemed to overshadow the others in the relief of symptoms of bronchial asthma. This reviewer sees little use for these drugs in asthma in competition with so many others of more valuable effect, unless there is an instance where the specific action of the antihistamine might be considered to be of some exact consequence.

Benadryl was used by Bignall and Crofton[6] in an effort to control streptomycin side effects. The nausea and vomiting was controlled in three test patients, but the giddiness was not relieved. Dramamine as a preventative for motion sickness has been introduced rather recently. Gray and Carliner[43] found that this drug was beneficial upon testing its use on a large number of soldiers in transport. There were no toxic manifestations of consequence. The optimal dosage was 100 mg. four times daily. If the patients were too ill to retain the oral dosage, good relief was experienced with rectal administration. It is doubted if correct control was employed in the comparative results with the use of placeboes. Eight cases of acute nephritis were treated with Neo-Antergan by Craig, Clark and Chalmers.[24] They found that the symptoms of the disease were of shorter duration in the eight children treated than in the control, untreated group. When Pyribenzamine was discontinued an acute delirium cleared in the patient described by Lipp, Grug and Glenn.[73] The medication was originally given for drug dermatitis, but delusions and hallucinations were noted approximately forty-eight hours after the initial dosage. Perazil has been investigated by Jaros.[61] This drug in a dosage of 50 mg. daily, or twice daily, has been the source of some prolonged relief to the author's patients, even though it is not enteric-coated. Personal experience of this reviewer reveals that the drug was of distinct benefit in seasonal hay fever and less so in acute urticaria. Leopold[71] could find no marked change in the blood counts following the use of Benadryl for as long as seventeen months. No purpura nor hemorrhage occurred and readministration of the drug after a free period did not produce any further change. Intravenous injection of Benadryl produced no change of note with smaller dosages in the blood pressure of Mackmull's patients.[78] Dosages of 100, 200, and 300 mg. did tend to elevate the blood pressure and produce significant changes in the electrocardiographic tracings. These larger dosages should not be used in hypertensive patients. Blackman and Hayes[8] report a fatality with the use of Benadryl in the therapy of an acute attack of bronchial asthma. The primary cause of death was felt to have been a severe depression of the central nervous system with the drug being responsible for the depression. Benadryl decreased the size of the tuberculin reaction in the guinea pigs studied by Sarber.[106] The test animals were injected with serial dilutions of tuberculin before and after the administration of Benadryl which was continued throughout the forty-eight-hour period of delayed reaction. The incidence of necrosis was markedly reduced with the medication. The Mantoux test in humans was diminished during antihistamine therapy. Judd and Henderson[63] feel that encouraging results in human tuberculosis were obtained with this form of treatment. One wonders whether such a paper

should be given publicity or not, with the thought that a lay publication may gain the knowledge that rest, and other forms of accepted therapy need not be rigid. Spain and Pflum[116] report the findings of the Committee on Therapy of the American Academy of Allergy. Benadryl, Pyribenzamine, Neo-Antergan, Hydryllin and Trimeton were studied. Best results were reported in seasonal hay fever and urticaria. The committee advised against the substitution of these drugs in place of specific immunization or the use of epinephrine and ephedrine.

The use of the antihistaminic drugs in the aborting of common colds has received good publicity because of the inability of other measures to withstand the pressure of constant failure. Brewster[14] feels that the initial phase of a common cold is an allergic reaction. He studied 572 patients with symptoms characteristic of the common upper respiratory infection; nineteen or twenty-one patients were cured when the antihistaminic drug was given within one hour after the onset of initial symptoms; 116 patients (74 per cent) were cured when the drug was instituted within six hours of symptoms onset. The effectiveness of the therapy was inversely proportional to the lapse of time following the onset of symptoms to the initial dosage of the antihistaminic medication. Pyribenzamine was thought by Gordon[42] to be the best drug of three—Benadryl, Pyribenzamine, Thephorin—in aborting the symptoms of a common cold. Eighty-five per cent of 500 patients were made more comfortable and experienced shorter convalescent periods than did those untreated patients. The importance of these findings to the larger industries has been demonstrated by Murray.[86] He has noted 494 results of 510 treated patients; 314 of the 494 were cured in three days; eighty-three were improved with their symptoms having a duration of only six to seven days; ninety-seven patients received no benefit, and twenty-two of these failures possessed an idiosyncrasy for the Pyribenzamine used in therapy. Of the total treated, only seven missed any work, with the remainder being able to carry on their usual duties in spite of symptoms and treatment.

The necessity of careful interpretation of positive food tests in asthmatic children is discussed in an editorial.[33] Hill is quoted as stating that only about 20 per cent of positive tests are of clinical value and the importance of pollen and other environmental allergens demands much more attention in this regard. The relative importance of each positive reaction, inhalant or food, should be carefully appraised in the light of all accumulated findings in the individual problem. Uncommon reactions to uncommon foods are the subject of a paper by Langley.[67] He cites five case histories to show that some patients will respond in most unusual manners. His patients possessed clinical reactions to carrot and fish. Shock resulted from testing the first patient with an intradermal carrot extract. This should emphasize to all practicing allergists the danger of using the intradermal test without the protection of a previously administered scratch procedure. Langley's other patients demonstrated petit mal attacks from orange juice ingestion, from chocolate and celery use, and asthma of alarming degree from chocolate. Desensitization attempt by the oral route was a failure for this latter patient. A food discussion of gastrointestinal allergy with illustrative case reports is the basis of an article by Tuft.[125]

Though the general opinion is prevalent that allergy *per se* does not produce ulcer lesions, food allergy can provoke similar distress and symptoms. Where the x-ray evidence of ulcer is not demonstrable, food sensitivity must be differentiated from the organic pathology. It is recognized that there is considerable evidence in support of food allergy as a cause, actual and contributing, in irritable colon and mucous colitis. Even in chronic ulcerative colitis, the allergic factor cannot be overlooked, particularly if the history seems to point in that direction. Milk and wheat were thought by this author to be most frequently involved.

Vegetable gums in the etiology of allergic disorders may produce their results by ingestion, inhalation or contact. Gelfand[39] reports that the chief manifestations of

sensitivity are perennial rhinitis, asthma, dermatitis, urticaria and gastrointestinal distress. Karaya, tragacanth and arabic are the most important and most frequently used commercial gums. They are contained in certain foods to add bulk, thickness and binding qualities. Gum arabic is a common component of most adhesives, with gum tragacanth being used often in cosmetic and pharmaceutical manufacturing. Karaya is employed primarily in wave sets, hair dressings, and other lotions for external application. The widespread use of these gums makes it hazardous for the sensitive patient. The small bowel is believed by Tallant and his co-workers[121] to be involved in gastrointestinal food allergy. Upon feeding a special barium-allergen mixture to twelve patients, narrowing, segmentation and scattering were found in the small bowel on x-ray. Control patients were examined using a barium-water mixture. These bowel changes were not considered as specific but they were of significance in view of the normal pictures seen with the control feedings. Patients with allergic colitis do not have protruberant abdomens and are usually well nourished with no atrophy of the buttocks. The opinion of Lapin and Weissberg[68] is thus expressed in support of the use of sigmoidoscopic examination as an easy means of diagnosis. Seldom is hospitalization necessary for these patients. Three cases are reported in whom elimination diets and antihistaminic drugs were sources of palliative and prolonged relief. Price, Urbach et al[92] have shown excellent results with the use of propeptans in food allergy. Their findings are described in seven of ten patients with gastrointestinal symptoms due to sensitivity to ingested food. The three patients who failed to benefit from this method of therapy were thought to possess severe psychiatric disturbances. Under propeptan management, x-ray abnormalities of the gastrointestinal tract almost disappeared.

Davison[28] believes that when other methods of relief are adjudged failures, a course of histamine therapy is indicated in the migrainous patient. The intravenous route is to be preferred but this may be supplemented or replaced by the subcutaneous route if the former is impossible. Some patients have remained free of attacks for many months, and others have had a recurrence precipitated by allergic, physical or psychosomatic factors. Cunningham,[26] on the other hand, does not feel that histamine has been successful in his practice. Most of the patients he has seen with migraine have had their symptoms on a basis of allergy, until proven otherwise. The fact that histamine therapy is not a cure, but a procedure that must be given indefinitely is disturbing to this author. All other physical and organic factors should first be ruled in or out before any decision as to the cause of the migraine attacks has been ascertained. The value of thorough skin testing in the search for relief in migraine has been given impetus by King.[66] He has described a patient with recurrent, typical migraine in whom strict dietary management—based on the results of skin tests—and dust therapy has been successful in aborting and preventing the incapacitating attacks. Ogden[87] published six case reports wherein the headaches were due to dust sensitivity and adequate therapy was responsible for good relief. Most of his patients had been long in the use of nasal medication for the relief of associated nasal symptoms. Grenfell[45] has used nicotinic acid to relieve fifteen patients with typical migraine seizures. This medication was given thirty-one times to these patients and was successful in thirteen occasions. No toxic manifestations were encountered and no change was noted in blood pressure nor pulse either during or after the administration. For this reason, complicating heart or vascular disease was not a contraindication to the therapy. No attempt was made nor considered to prevent recurrences of the attacks. Marcussen and Wolff[81] feel that the therapy of migraine resides in two categories: treatment of the individual and prevention of further complaints. Intracranial vasoconstriction is considered as pre-headache phenomena with the onset of the headache being associated with vasodilation. The best method of attack-relief was thought to be ergotamine tartrate. The removal of stress seemed to reduce the frequency of attacks inasmuch

as emotional reactions, fatigue and accumulated tension added up to the typical parade of symptoms called migraine. That the above authors may misunderstand the true mechanism of the attack of migraine has been suggested by Waldbott.[129] He thinks that a pure psychoneurotic approach to this question is misleading. His letter has complained of the lack of consideration and mention of allergy in the above article on migraine. Friedman, Brenner and Carter[37] express themselves that trauma and psychoneurosis are the two most common causes of chronic headache. They reported 521 patients, with 494 receiving combined psychotherapy and pharmacotherapy and twenty-seven treated with psychotherapy alone. Of the drugs used, the analgesics were determined to be most efficacious. Because of the similarity of results from drug therapy, the authors suggest that the above two common types of chronic headache are closely related as to causative mechanisms.

A very good description of the attacks with the history of the headaches is considered of the utmost importance by Horton.[57] For example, the time of onset is of the greatest significance. Night attacks are typical of histamine cephalalgia. Pain in the head arises from the following sources: the tissues covering the cranium, cranial periosteum and endosteum, and certain intracranial structures. The cranium, brain, dura, pia-arachnoid, choroid plexus and ependymal lining of the ventricle are insensitive to pain. Practically all headaches, regardless of type, are vascular in origin. Sixteen illustrative case reports are given as examples of the various types of headaches, with notes indicating the proper diagnostic and therapeutic approach for each occasion. This same author, with Macy,[77] lists the five fundamental features of migraine: periodicity, cephalalgia, gastrointestinal disturbances, cortical changes and a positive familial history of migraine attacks. Two series of a total of 144 cases are reviewed to establish the effect of histamine therapy. Most improvement was noted in the atypical cases of migraine—those in whom a periodic cephalalgia is associated with any of the above three factors. Combined subcutaneous and intravenous therapy was most beneficial. Recurrence of symptoms following treatment was the rule unless therapy was continued. Hansel[49] feels that Cafergone, a combination of ergotamine tartrate (1 mg.) with caffeine (100 mg.) is superior to the use of the former preparation by itself. The medication is available for oral usage. Cafergone was found to be effective in the relief of all types of headache, especially in the atypical and typical histaminic cephalalgia. Gynergen was thought to be superior, however, for the relief of the acute attack, if it could be given at the onset of symptoms. Ireland[60] has reported 199 cases of Ménière's disease, with ninety of them being treated with resection of the eighth nerve. Destruction of the labyrinth was done in thirty-three patients. Though both methods were beneficial, medical management consisting of sedation, sodium restriction, and limitation of fluid intake gave satisfactory relief in about 90 per cent of the cases. Histamine therapy was of some value, relieving nine of eleven patients.

This review of miscellaneous literature in allergy would hardly be complete without calling attention to the listing compiled by Bowen and Efron.[11] This is of importance because of the great consumption of acetylsalicylic acid and the frequency with which this use is encountered in allergy.

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SUBCUTANEOUS EMPHYSEMA COMPLICATING BRONCHIAL ASTHMA

(Continued from Page 784)

part of face, the anterior and posterior portions of the chest, the axillary regions, abdomen, back and in the right inguinal region. He felt better, ate some food and became cheerful. A heavy mucoid material was discharged from both nostrils. His progress continued steadily. Ephedrine, aminophylline and codeine administered orally were sufficient. The subcutaneous emphysema disappeared slowly; that in the inguinal region persisted for seventeen days, and the axillary and supraclavicular areas persisted for ten to fourteen days.

SUMMARY

1. Two cases of subcutaneous emphysema complicating an acute exacerbation of bronchial asthma are reported.

2. Recovery followed bed rest and symptomatic management.

3. The severe symptoms of asthma abated with the occurrence of the subcutaneous emphysema.

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News Items

INTERNATIONAL ASSOCIATION OF ALLERGISTS

The following societies are official members of The International Association of Allergists:

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SOCIEDAD ESPANOLA DE ALERGIA: President, Dr. O. Jimenez Diaz, General Mola 9, Madrid, Espana (Spain).

SOUTHERN SWEDISH ALLERGY FORUM: Chairman, Prof. Gösta Dohlman, Dept. of Otolaryngology, Lund University Hospital, Lund, Sweden.

SWEDISH ASSOCIATION OF ALLERGISTS: President, Prof. Sven Hellerstrom, Karolinska Sjukhuset, Stockholm 60, Sweden.

SWISS ALLERGY SOCIETY: President, Prof. Dr. A. S. Grumbach, Hygiene-Institut der Universitat, Gloriastr. 32, Zurich 7, Switzerland.

THE AMERICAN COLLEGE OF ALLERGISTS: President, Dr. Jonathan Forman, 956 Bryden Road, Columbus, Ohio.

THE AMERICAN SOCIETY OF OPHTHALMOLOGIC AND OTOLARYNGOLOGIC ALLERGY: President, Dr. Rea E. Ashley, 384 Post Street, San Francisco, California.

SOUTHEASTERN ALLERGY ASSOCIATION

The fifth annual meeting of the Southeastern Allergy Association will be held at the Columbia Hotel, Columbia, South Carolina, on Saturday and Sunday, February 11 and 12, 1950. Please note that the month has been changed because of changes made in the meeting dates of the American Academy of Allergy and the American College of Allergists. This puts the meeting of the Southeastern Allergy Association midway between the two.

The guest speakers will be Dr. Jonathan Forman, President of the American College of Allergists, and Dr. Theodore Squier, President-Elect of the American Academy of Allergy.

In view of the popularity of panel discussions, there will again be two, one on "Pediatric Allergy" with Dr. Lewis Hoppe of Atlanta as co-ordinator, and the

other on "Office Procedure" with Dr. J. Warrick Thomas of Richmond as co-ordinator.

Members who are desirous of presenting papers at this meeting are urged to contact the secretary at an early date. Each paper will be allowed 20 minutes for presentation and 10 minutes for discussion.

For further information, please write directly to the Secretary, Dr. Katharine Baylis MacInnis, 1515 Bull Street, Columbia, South Carolina.

NEW YORK ALLERGY SOCIETY AWARD

The Committee on Annual Award of the New York Allergy Society, Horace S. Baldwin, Chairman, announces a prize of $150.00 for the best essay of merit by a student of a medical school in Greater New York City. For the coming year 1949-1950, the topic selected by the Annual Award Committee is "Bronchial Asthma and its Relation to Foci of Infection in the Upper Respiratory Tract." The essay should not exceed 15,000 words. It should contain some reference to clinical experience gained in the medical school or hospital, and references to published work should be indicated in a Bibliography. It should be approved by the head of the department of medicine of the medical school in which the essayist is a student.

A report of original investigations in the fields of general allergy or of immunology, which the committee deems meritorious, will be given consideration equal to that of essays on the designated topic.

All essays must be sent to the Secretary of the New York Allergy Society, Dr. Frederick R. Brown, 39 West 55th Street, New York City prior to May 1, 1950.

PENNSYLVANIA ALLERGY ASSOCIATION

The fall meeting of the Pennsylvania Allergy Association was held in Pottsville, Pennsylvania, with Drs. Harold Abramson, James Flood, Bret Ratner, Harry Rogers, and Alexander Peters as the guest speakers. The following officers were elected for the ensuing year: President, Dr. Alexander Peters of Allentown; Vice President, Dr. Samuel Kaufman of Wilkes-Barre; Secretary-Treasurer, Dr. Ralph M. Mulligan of Reading. Drs. Lester Fowle of Lewisburg and James Mansmann of Pittsburgh were elected to the Board of Regents for a three-year term. Dr. Stephen Lockey of Lancaster was awarded the first Certificate of Merit for the most outstanding work in Allergy during the year 1949. Thirteen new members were elected to membership at this meeting.

The spring meeting of the Association will be held at the Bedford Springs Hotel in Bedford, Pennsylvania, on May 11, 1950. The spring meeting of the Pennsylvania Academy of Ophthalmology and Otolaryngology will be held at the same place on May 12, 13, and 14.

PHILADELPHIA ALLERGY SOCIETY

The Fifteenth Annual Scientific Meeting of the Philadelphia Allergy Society was held on October 26, 1949. Dr. Herman Gold, President, presided, with Dr. Samuel E. Rynes as Secretary. The following program was presented:

1. "The Prevention of Infectious Asthma" by A. E. Fishman, M.D.
2. "Inhalant Allergens as a Factor in Atopic Dermatitis. An Experimental Clinical Study," by Louis Tuft, M.D., Harold S. Tuft, M.D., and V. Muriel Heck, M.T.
3. "Dermatitis Venenata Due to Verbena Rigida Spreng" by Charles Bancroft, M.D.
4. Panel Discussion on Antihistamines in the 1949 Hay Fever Season. Trimeton, Decapryn, and Pyrrolazote by Alexander Sterling, M.D., Pyribenzamine and

Neo-Antergan by George Blumstein, M.D. Neohetramine by Louis Silcox, M.D. Chlor-Trimeton Maleate by Samuel E. Rynes, M.D.

5. "Roentgenographic Appearance of the Chest in Diseases Affecting the Peripheral Pulmonary Vessels," by Robert Phelps Barden, M.D., Assistant Professor of Radiology in the School of Medicine at the University of Pennsylvania.

CHICAGO SOCIETY OF ALLERGY

At a recent meeting of the Chicago Society of Allergy, the following officers were elected for the ensuing year: President, Dr. Morris A. Kaplan; President-Elect, Dr. Townsend B. Friedman; and Secretary-Treasurer, Dr. Theron G. Randolph.

NEW EQUIPMENT

A machine for cleaning hypodermic needles is now being manufactured and marketed by the Medical Equipment Laboratories, 5404 Sierra Vista Avenue, Los Angeles 38, California.

The Casady Hypodermic Needle Cleaner, invented by R. R. Casady, M.D., was developed to reduce the great amount of time now required for the manual cleaning of the ever increasing number of hypodermic needles being used. Equally important—it gives dependably clean needles.

This machine can cut the amount of time required to clean needles by as much as 80 per cent—and can deliver needles more thoroughly and effectively than is possible by hand methods.

In this machine the hubs of the needles are forcefully cleaned by an electrically driven swab. Then the needles are washed with three separate fluids, successively passed through the needles under 20 pounds pressure, followed by a stream of compressed air, leaving them dry and clean.

One hundred needles can be swabbed out, washed, rinsed and dried in nine minutes.

* * *

Philip M. Gottlieb, M.D., F.A.C.A., announces the removal of his offices for the practice of Allergy and Internal Medicine to 818 Medical Arts Building, Philadelphia 3, Pennsylvania.

* * *

As the ANNALS goes to press, we regretfully announce the deaths of two Fellows of the College—Dr. W. Byron Black, Kansas City, Missouri, who was President of the Hansel Foundation, and Dr. Arthur C. Kalisch, York, Pennsylvania, who was one of the charter members of the Pennsylvania Allergy Association. Their obituaries will appear in the January-February issue of the ANNALS.

* * *

ANNALS OF ALLERGY, 7:301-442 (May-June) 1949, was indexed in part under Current Medical Literature of the JAMA 141:796 (November 12) 1949 issue. The article by Judd and Henderson, "Use of Antihistaminic Drugs in Human Tuberculosis: Preliminary Report," and "Allergy and the Tonsil Problem in Children" by Clein were abstracted.

* * *

Dr. Harold A. Abramson has been appointed Chief of the Allergy Clinic at The Mount Sinai Hospital, New York, New York.

BOOK REVIEWS

PAVLOV, A BIOGRAPHY. By B. P. Babkin, M.D. 378 pages. Illustrated. $6.00. The University of Chicago Press.

The major and fundamental contributions of Pavlov to medicine are well known to all serious students of gastroenterology, neurology and psychiatry. Pavlov's fame, however, rests on a wider and more fundamental base than the mass accumulation of data because the principles and methods of scientific investigation which he established are of enduring importance and significance. This biography amply satisfies a long felt need for an authentic description of Pavlov as a man, the environment in which he worked and a critical summation of his contributions to medicine.

Professor Babkin, now of the Montreal Neurological Institute, is without doubt best qualified to write such a biography because he worked with Pavlov for many years, and has himself attained such eminence as a scientist in his own right that he is justly considered the most famous of Pavlov's students. One would therefore expect such an author to write a creditable biography. Professor Babkin has done much more than this. He has written such a masterful exposition that his text might well serve as an example to other biographers of scientists.

Many facts of Pavlov's personal life are here presented for the first time. His relations with his colleagues and contemporaries are described impartially with revealing and amusing anecdotes. The sections summarizing and analyzing Pavlov's work, and showing its impact on Pavlov's contemporaries as well as its influence on present day scientists, are particularly well done.

This book is enjoyable and profitable reading for any intelligent layman. It deserves careful reading by everyone who has an interest in the medical sciences. It is required reading for every physician who seeks an understanding of his own profession and the role of Pavlov's monumental contributions.

SKIN SENSITIZATION TO BAL OINTMENT

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